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(71) Applicant *(for all designated States except US)*: **ACTELION PHARMACEUTICALS LTD** [CH/CH]; Actelion LTD, Gewerbestrasse 16, CH-4123 Allschwil (CH).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **BOSS, Christoph** [CH/CH]; Muesmattweg 98, CH-4123 Allschwil (CH). **FISCHLI, Walter** [CH/CH]; Obertorweg 64, CH-4123 Allschwil (CH). **MEYER, Solange** [FR/FR]; 10A, rue du ruisseau, F-68440 Schlierbach (FR). **RICHARD-BILDSTEIN, Sylvia** [FR/FR]; 34A, rue d'Ottmarsheim, F-68170 Rixheim (FR). **WELLER, Thomas** [CH/CH]; Hoelzlistrasse 58, CH-4102 Binningen (CH).

(74) Agent: **HOFMANN, Dieter**; StratAll, Therwilerstrasse 87, CH-4153 Reinach (CH).

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(54) Title: SUBSTITUTED AMINO-AZA-CYCLOALKANES USEFUL AGAINST MALARIA

(57) Abstract: The invention relates to novel compounds which are substituted amino-aza-cycloalkane derivatives of the general formula I. The invention also concerns related aspects including processes for the preparation of the compounds, pharmaceutical compositions containing one or more compounds of general formula I and especially their use as inhibitors of the plasmodium falciparum protease plasmepsin II or related aspartic proteases.

SUBSTITUTED AMINO-AZA-CYCLOALKANES USEFUL AGAINST MALARIA

The invention relates to novel compounds which are substituted amino-aza-cycloalkane derivatives of the general formula I. The invention also concerns related aspects including processes for the preparation of the compounds, pharmaceutical compositions containing one or more compounds of general formula I and especially their use as inhibitors of the plasmodium falciparum protease plasmepsin II or related aspartic proteases.

Background of the invention:

Malaria is one of the most serious and complex health problems affecting humanity in the 21st century. The disease affects about 300 million people worldwide, killing 1 to 1.5 million people every year. Malaria is an infectious disease caused by four species of the protozoan parasite Plasmodium, P. falciparum being the most severe of the four. All attempts to develop vaccines against P. falciparum have failed so far. Therefore, therapies and preventive measures against malaria are confined to drugs. However, resistance to many of the currently available antimalarial drugs is spreading rapidly and new drugs are needed.

P. Falciparum enters the human body by way of bites of the female anophelino mosquito. The plasmodium parasite initially populates the liver, and during later stages of the infectious cycle reproduces in red blood cells. During this stage, the parasite degrades hemoglobin and uses the degradation products as nutrients for growth [1]. Hemoglobin degradation is mediated by serine proteases and aspartic proteases. Aspartic proteases have been shown to be indispensable to parasite growth. A non-selective inhibitor of aspartic proteases, Pepstatin, inhibits the growth of P. falciparum in red blood cells in vitro. The same results have been obtained with analogs of pepstatin [2], [3]. These results show that inhibition of parasite aspartic proteases interferes with the life cycle of P. falciparum. Consequently, aspartic proteases are targets for antimalarial drug development.

The present invention relates to the identification of novel low molecular weight, non-peptidic inhibitors of the plasmodium falciparum protease plasmepsin II or other related aspartic proteases to treat and/or prevent malaria.

The compounds of general formula I were tested against plasmepsin II, HIV-protease, human cathepsin D, human cathepsin E and human renin in order to determine their biological activity and their selectivity profile.

In vitro Assays:

The fluorescence resonance energy transfer (FRET) assay for HIV, plasmepsin II, human cathepsin D and human cathepsin E.

The assay conditions were selected according to reports in the literature [4 - 7]. The FRET assay was performed in white polysorp plates (Fluoronunc, cat n° 437842 A). The assay buffer consisted of 50 mM Na acetate pH 5, 12,5% glycerol, 0.1% BSA + 392 mM NaCl (for HIV-protease).
The incubates per well were composed of:

- 160 µl buffer
- 10 µl inhibitor (in DMSO)
- 10 µl of the corresponding substrate in DMSO (see table A) to a final concentration of 1 µM
- 20 µl of enzyme to a final amount of x ng per assay tube (x = 10 ng/assay tube plasmepsin II, x = 100 ng/assay tube HIV-protease, x = 10 ng/assay tube human cathepsin E and x = 20 ng/assay tube human cathepsin D)

The reactions were initiated by addition of the enzyme. The assay was incubated at 37°C for 30 min (for human cathepsin E), 40 min (for plasmepsin II and HIV-protease) or 120 min (for human cathepsin D). The reactions were stopped by adding 10% (v/v) of a 1 M solution of Tris-base. Product-accumulation was monitored by measuring the fluorescence at 460 nm.

Auto-fluorescence of all the test substances is determined in assay buffer in the absence of substrate and enzyme and this value was subtracted from the final signal.

Aspartyl protease	substrate		enzyme concentration ng/at (nM)	Buffer	pH	incubation time minutes
	sequence	substrate concentration µM				
HIV	Dabcyl-Abu-SQNY:PIVN-EDANS	1	100 (22.5)	50 mM Na acetate ; 12,5 % glycerol ; 0.1 % BSA 392 mM NaCl	5	40
Plasmepsin II	Dabcyl-ERNleF:LSFP-EDANS	1	10 (1.25)	50 mM Na acetate ; 12,5 % glycerol ; 0.1% BSA	5	40
h Cathepsin D	Dabcyl-ERNleF:LSFP-EDANS	1	20 (2.5)	50 mM Na acetate ; 12,5 % glycerol ; 0.1% BSA	5	120
h Cathepsin E	Dabcyl-ERNleF:LSFP-EDANS	1	10 (1.25)	50 mM Na acetate ; 12,5 % glycerol ; 0.1% BSA	5	30

Table A: Summary of the conditions used for the aspartyl proteases fluorescent assays. (at = assay tube)

Enzymatic in vitro assay for renin:

The enzymatic in vitro assay was performed in polypropylene plates (Nunc, Cat No 4-42587A). The assay buffer consisted of 100 mM sodium phosphate, pH 7.4, including 0.1% BSA. The incubates were composed of 190 µL per well of an enzyme mix and 10 µL of renin inhibitors in DMSO. The enzyme mix was premixed at 4°C and composed as follows:

- human recombinant renin (0.16 ng/mL)
- synthetic human tetradecapeptide renin substrate (0.5 µM)
- hydroxyquinoline sulfate (0.1 mM)

The mixtures were then incubated at 37°C for 3 h.

To determine the enzymatic activity and its inhibition, the accumulated Angiotensin I was detected by an enzyme immunoassay (EIA). 10 µL of the incubates or standards were transferred to immuno plates which were previously coated with a covalent complex of Angiotensin I and bovine serum albumin (Ang

I – BSA). 190 µL of Angiotensin I-antibodies were added and a primary incubation made at 4°C over night. The plates were washed 3 times and then incubated for one hour at room temperature with a *biotinylated anti-rabbit antibody.* Thereafter, the plates were washed and incubated at room temperature for 30 min with a *streptavidin-peroxidase complex.* After washing the plates, the *peroxidase substrate* ABTS (2.2'-Azino-di-(3-ethyl-benzthiazolinsulfonate), was added and the plates incubated for 10-30 min at room temperature. After stopping the reaction with 0.1 M citric acid pH 4.3 the plate is evaluated in a microplate reader at 405 nm.

Table 1: IC_{50} values (nM) for selected compounds on plasmepsin II:

Example Nr:	IC_{50} (nM) on plasmepsin II
Example 1	70
Example 2	1500
Example 3	1700
Example 6	1800
Example 7	462
Example 9	1700
Example 10	1200
Example 11	3200
Example 13	2400
Example 14	84
Example 15	1300
Example 16	1300
Example 18	148
Example 22	793
Example 24	427
Example 25	220
Example 26	497
Example 30	695
Example 31	210
Example 32	18
Example 33	96
Example 34	1970
Example 35	1700
Example 36	164
Example 37	1530

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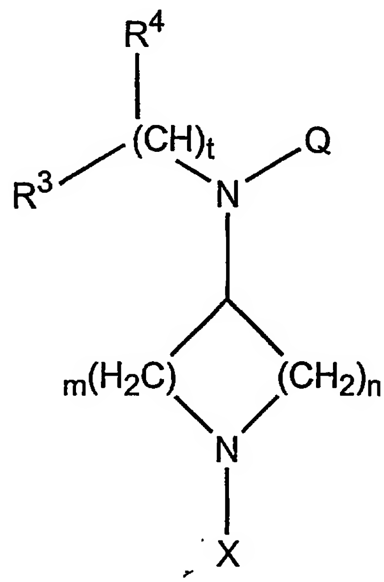
The present invention relates to novel, low molecular weight organic compounds, which are substituted amino-aza-cycloalkanes of the **general formula I**:



General Formula I

wherein

Q represents $-SO_2-R^1$; $-CO-R^1$; $-CO-NH-R^1$; $-CO-N(R^1)(R^2)$; $-CO-OR^1$; $-(CH_2)_p-R^1$; $-(CH_2)_p-CH(R^1)(R^2)$;

X represents $-SO_2-R^1$; $-CO-R^1$; $-CO-NH-R^1$; $-CO-N(R^1)(R^2)$; $-CO-OR^1$; $-(CH_2)_p-R^1$; $-(CH_2)_p-CH(R^1)(R^2)$; hydrogen;

R^1, **R^2** and **R^3** represent lower alkyl; lower alkenyl; aryl; heteroaryl; cycloalkyl; heterocyclyl; aryl-lower alkyl; heteroaryl-lower alkyl; cycloalkyl-lower alkyl; heterocyclyl-lower alkyl; aryl-lower alkenyl; heteroaryl-lower alkenyl; cycloalkyl-lower alkenyl; heterocyclyl-lower alkenyl;

R^4 represents hydrogen; $-CH_2-OR^5$; $-CO-OR^5$;

R^5 represents hydrogen, lower alkyl; cycloalkyl; aryl; heteroaryl; heterocyclyl; cycloalkyl-lower alkyl; aryl-lower alkyl; heteroaryl-lower alkyl; heterocyclyl-lower alkyl;

t represents the whole numbers 0 (zero) or 1 and in case t represents the whole number 0 (zero), R^4 is absent;

m represents the whole numbers 2, 3 or 4;

n represents the whole numbers 1 or 2;

p represents the whole numbers 0 (zero), 1 or 2;

and pure enantiomers, mixtures of enantiomers, pure diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates and pharmaceutically acceptable salts thereof

In the definitions of the **general formula I** – if not otherwise stated – the expression lower means straight and branched chain groups with one to seven carbon atoms, preferably 1 to 4 carbon atoms which may optionally be substituted with hydroxy or lower alkoxy. Examples of lower alkyl groups are methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec.-butyl, tert.-butyl, pentyl, hexyl, heptyl. Examples of lower alkoxy groups are methoxy, ethoxy, propoxy, iso-butoxy, sec.-butoxy and tert.-butoxy etc. Lower alkylendioxy-groups as substituents of aromatic rings onto two adjacent carbon atoms are preferably methylen-dioxy and ethylen-dioxy. Lower alkylen-oxy groups as substituents of aromatic rings onto two adjacent carbon atoms are preferably ethylen-oxy and propylen-oxy. Examples of lower alkanoyl-groups are acetyl, propanoyl and butanoyl. Lower alkenylen means e.g. vinylen, propenylen and butenylen.

The expression **cycloalkyl**, alone or in combination, means a saturated cyclic hydrocarbon ring system with 3 to 6 carbon atoms , e.g. cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl which may be substituted with lower alkyl groups.

The expression **heterocyclyl**, alone or in combination, means saturated or unsaturated (but not aromatic) five-, six- or seven-membered rings containing one or two nitrogen, oxygen or sulfur atoms which may be the same or different and which rings may be substituted with lower alkyl, lower alkenyl, aryl, aryl-lower alkyloxy, aryl-oxy, amino, bis-(lower alkyl)-amino, alkanoyl-amino, halogen, nitro, hydroxy, lower alkoxy, phenoxy; examples of such rings are morpholinyl, piperazinyl, tetrahydropyranyl, dihydropyranyl, 1,4-dioxanyl, pyrrolidinyl, tetrahydrofuranyl, dihydropyrrolyl, imidazolidinyl, dihydropyrazolyl, pyrazolidinyl etc. and substituted derivatives of such type rings with substituents as outlined hereinbefore.

The expression **heteroaryl**, alone or in combination, means six-membered aromatic rings containing one to four nitrogen atoms; benzofused six-membered aromatic rings containing one to three nitrogen atoms; five-membered aromatic rings containing one oxygen, one nitrogen or one sulfur atom; benzo-fused five-membred aromatic rings containing one oxygen, one nitrogen or one sulfur atom; five membered aromatic rings containig one oxygen and one nitrogen atom and benzo fused derivatives thereof; five membred aromatic rings containing a sulfur and nitrogen or oxygen atom and benzo fused derivatives thereof; five membered aromatic rings containing three nitrogen atoms and benzo fused derivatives thereof or the tetrazolyl ring; examples of such rings are furanyl, thienyl, pyrrolyl, pyridinyl, indolyl, quinolinyl, isoquinolinyl, dihydroquinolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, imidazolyl, triazinyl, thiazinyl, pyridazinyl, oxazolyl, etc. whereby such ring systems may be mono-, di- or tri-substituted with aryl; aryloxy, aryl-lower alkyl-oxy, lower alkyl; lower alkenyl; lower alkyl-carbonyl; amino; lower alkyl-amino; bis-(lower-alkyl)-amino; lower alkanoyl-amino; ω-amino-lower alkyl; halogen; hydroxy; carboxyl; lower alkoxy; vinyloxy; allyloxy; ω-hydroxy-lower alkyl; nitro; cyano; amidino; trifluoromethyl; lower alkyl-sulfonyl etc.

The expression **aryl**, alone or in combination, means six membered aromatic rings and condensed systems like naphthyl or indenyl etc. whereby such ring

systems may be mono-, di- or tri-substituted with aryl, aryloxy, aryl-lower alkyloxy, lower alkyl, lower alkenylen, lower alkyl-carbonyl, aryl-carbonyl, amino, lower alkyl-amino, aryl-amino, bis-(lower-alkyl)-amino, lower alkanoyl-amino, ω-amino-lower alkyl, halogen, hydroxy, carboxyl, lower alkoxy, vinyloxy, allyloxy, ω-hydroxy-lower alkyl, ω-hydroxy-lower alkoxy, nitro, cyano, amidino, trifluoromethyl, lower alkyl-sulfonyl etc.
It is understood that the substituents outlined relative to the expressions cycloalkyl, heterocyclyl, heteroaryl and aryl have been omitted in the definitions of the general formulae I to V and in claims 1 to 5 for clarity reasons but the definitions in formulae I to V and in claims 1 to 5 should be read as if they are included therein.

The expression pharmaceutically acceptable salts encompasses either salts with inorganic acids or organic acids like hydrochloric or hydrobromic acid; sulfuric acid, phosphoric acid, nitric acid, citric acid, formic acid, acetic acid, maleic acid, tartaric acid, methylsulfonic acid, p- toluolsulfonic acid and the like or in case the compound of formula I is acidic in nature with an inorganic base like an alkali or earth alkali base, e.g. sodium hydroxide, potassium hydroxide, calcium hydroxide etc.

The compounds of the general formula I can contain one or more asymmetric carbon atoms and may be prepared in form of optically pure enantiomers, diastereomers, mixtures of diastereomers, diastereomeric racemates and mixtures of diastereomeric racemates.
The present invention encompasses all these forms. Mixtures may be separated in a manner known per se, i.e. by column chromatography, thin layer chromatography, HPLC, crystallization etc.

The compounds of the general formula I and their pharmaceutically acceptable salts may be used as therapeutics e.g. in form of pharmaceutical compositions. They may especially be used to in prevention or treatment of malaria. These compositions may be administered in enteral or oral form e.g. as tablets, dragees, gelatine capsules, emulsions, solutions or suspensions, in nasal form

like sprays or rectally in form of suppositories. These compounds may also be administered in intramuscular, parenteral or intraveneous form, e.g. in form of injectable solutions.

These pharmaceutical compositions may contain the compounds of formula I as well as their pharmaceutically acceptable salts in combination with inorganic and/or organic excipients which are usual in the pharmaceutical industry like lactose, maize or derivatives thereof, talcum, stearinic acid or salts of these materials.

For gelatine capsules vegetable oils, waxes, fats, liquid or half-liquid polyols etc. may be used. For the preparation of solutions and sirups e.g. water, polyols saccharose, glucose etc. are used. Injectables are prepared by using e.g. water, polyols, alcohols, glycerin, vegetable oils, lecithin, liposomes etc. Suppositories are prepared by using natural or hydrogenated oils, waxes, fatty acids (fats), liquid or half-liquid polyols etc.

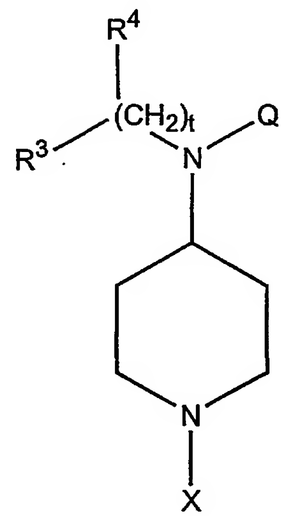
The compositions may contain in addition preservatives, stability improving substances, viscosity improving or regulating substances, solubility improving substances, sweeteners, dyes, taste improving compounds, salts to change the osmotic pressure, buffer, anti-oxidants etc.

The compounds of formula I may also be used in combination with one or more other therapeutically useful substances e. g. with other antimalarials like quinolines (quinine, chloroquine, amodiaquine, mefloquine, primaquine, tafenoquine etc), peroxide antimalarials (artemisinin derivatives), pyrimethamine-sulfadoxine antimalarials (e.g. Fansidar etc), hydroxynaphtoquinones (e.g. atovaquone etc.), acroline-type antimalarials (e. g. pyronaridine etc) etc.

The dosage may vary within wide limits but should be adapted to the specific situation. In general the dosage given in oral form should daily be between about 3 mg and about 3 g, peferably between about 10 mg and about 1 g, especially preferred between 5 mg and 300 mg, per adult with a body weight of about 70

kg. The dosage should be administered preferably in 1 to 3 doses per day which are of equal weight. As usual, children should receive lower doses which are adapted to body weight and age.

Preferred compounds are compounds of the **formula II**



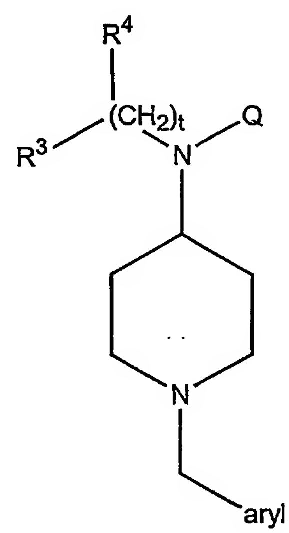
Formula II

wherein

X, Q, t, R^3 and **R^4** are as defined in general formula I above

and pure enantiomers, mixtures of enantiomers, pure diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates and pharmaceutically acceptable salts thereof.

Also preferred compounds are compounds of **formula III**



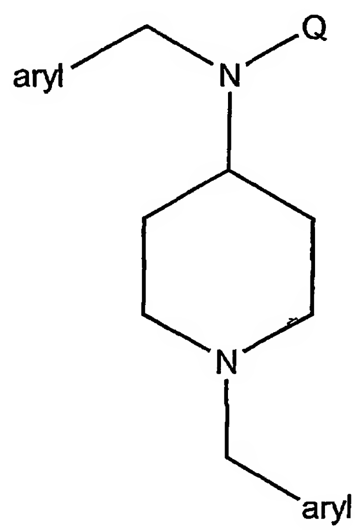
Formula III

wherein

Q, **t**, $\mathbf{R^3}$ and $\mathbf{R^4}$ are as defined in general formula I above

and pure enantiomers, mixtures of enantiomers, pure diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates and pharmaceutically acceptable salts thereof.

Especially preferred are also compounds of the **formula IV**



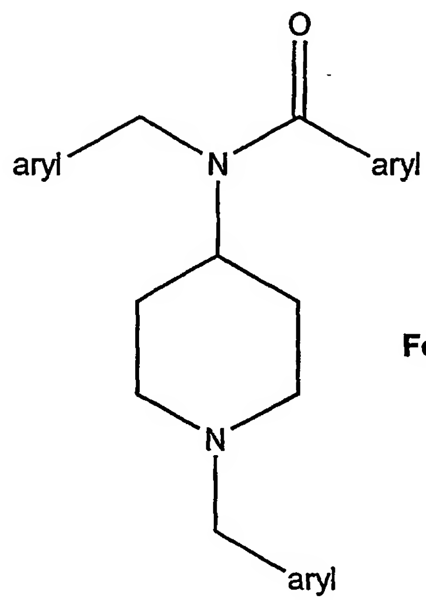
Formula IV

wherein

Q is as defined in general formula I above

and pure enantiomers, mixtures of enantiomers, pure diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates and pharmaceutically acceptable salts thereof.

Especially preferred are compounds of the **formula V**

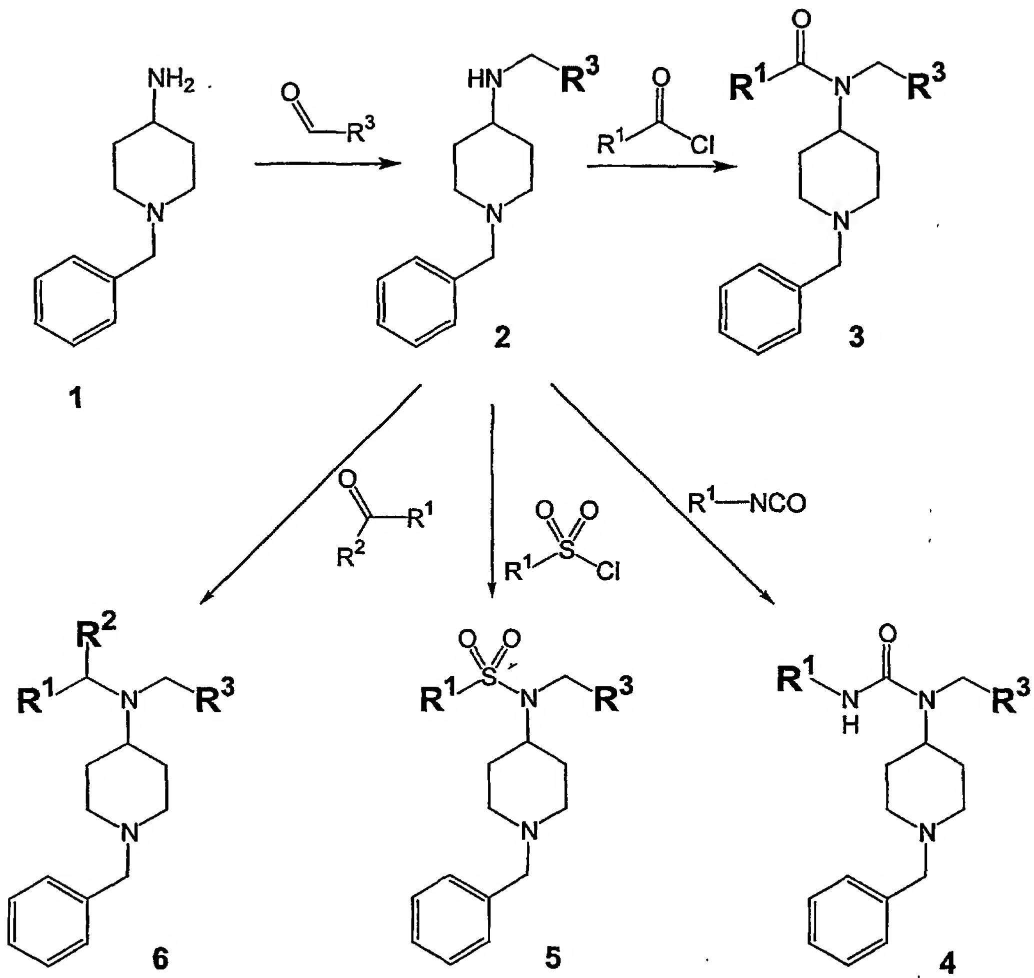


Formula V

and pure enantiomers, mixtures of enantiomers, pure diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates and pharmaceutically acceptable salts thereof.

The compounds of the **general formula I** of the present invention may be prepared according to the general sequences of reactions outlined below, wherein R^1, R^2, R^3, R^4, R^5, Q, X, t, m, n and p are as defined in general formula I above (for simplicity and clarity reasons, only parts of the synthetic possibilities which lead to compounds of formulae I to V are described). For general methods of certain steps see also pages 19 – 23.

Scheme 1: Preparation of substituted 4-amino-N-benzyl-piperidines:



Typical procedure for the reductive amination (Synthesis of compounds 2):

The amine (**1**) and the aldehyde {R^3-CHO} (1.5 eq.) are mixed in anhydrous methanol and stirred for 6 h. The mixture is then treated with sodium borohydride (1.5 eq.) and stirred for 2 h. Purified Amberlyst 15 or another suitable scavenger is added and the suspension is shaken for 12 h. The resin is then separated by filtration and washed with methanol. The secondary amine **2** is removed from the resin by adding a 2 M methanolic ammonia solution. The resin is drained after 30 min and washed with methanol. The filtrate is evaporated to yield the pure secondary amine **2**.

Typical procedure for the acylation (Synthesis of compounds **3**):

To a solution of the amine **2** in anhydrous ethyl acetate is added vacuum dried Amberlyst 21 or another suitable scavenger followed by the addition of the carboxylic acid chloride {R^1-(CO)-Cl} (1.5 eq.). After shaking the suspension for 2 h, an aliquot of water is added in order to hydrolyze the excess of the carboxylic acid chloride and shaking is continued for 1 h. The resin is then removed by filtration, washed with ethyl acetate and the solution is evaporated to yield the pure amide **3**.

The carboxylic acid chlorides {R_1-(CO)-Cl} may be obtained *in situ* from the corresponding carboxylic acid as described in the literature (i. e.: Devos, A.; Rémion, J.; Frisque-Hesbain, A.-M.; Colens,A.; Ghosez, L., *J. Chem. Soc., Chem. Commun.* **1979**, 1180).

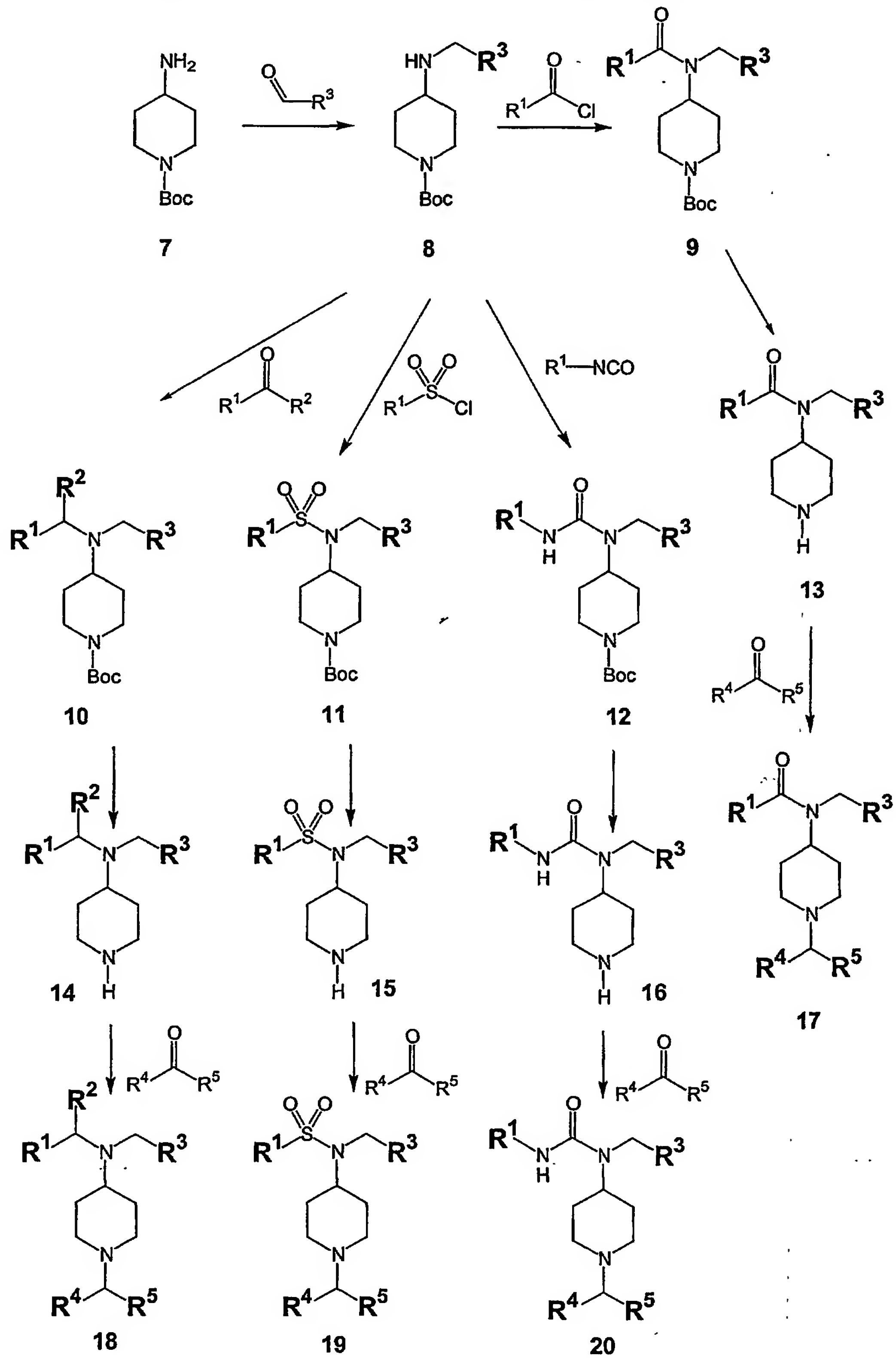
The synthesis of the sulfonamide derivatives **5** from the amine **2** is performed in analogy to the above described procedure.

The urea derivatives **4** are obtained by reaction of the amines **2** in dichloromethane, with one equivalent isocyanate.

Typical procedure for the second reductive amination (Synthesis of compound **6**):

The amine (**2**) and the aldehyde or the ketone {R_1R_2CO} (1.5 eq.) are mixed in anhydrous dichloromethane and sodium triacetoxyborohydride (1.3 eq.) is added. After stirring the solution for 48h, methanol is added and the reaction mixture is treated in the same manner as described for amines **2**.

Scheme 2: Preparation of substituted 4-amino-N-(lower alkyl-aryl)-piperidines:

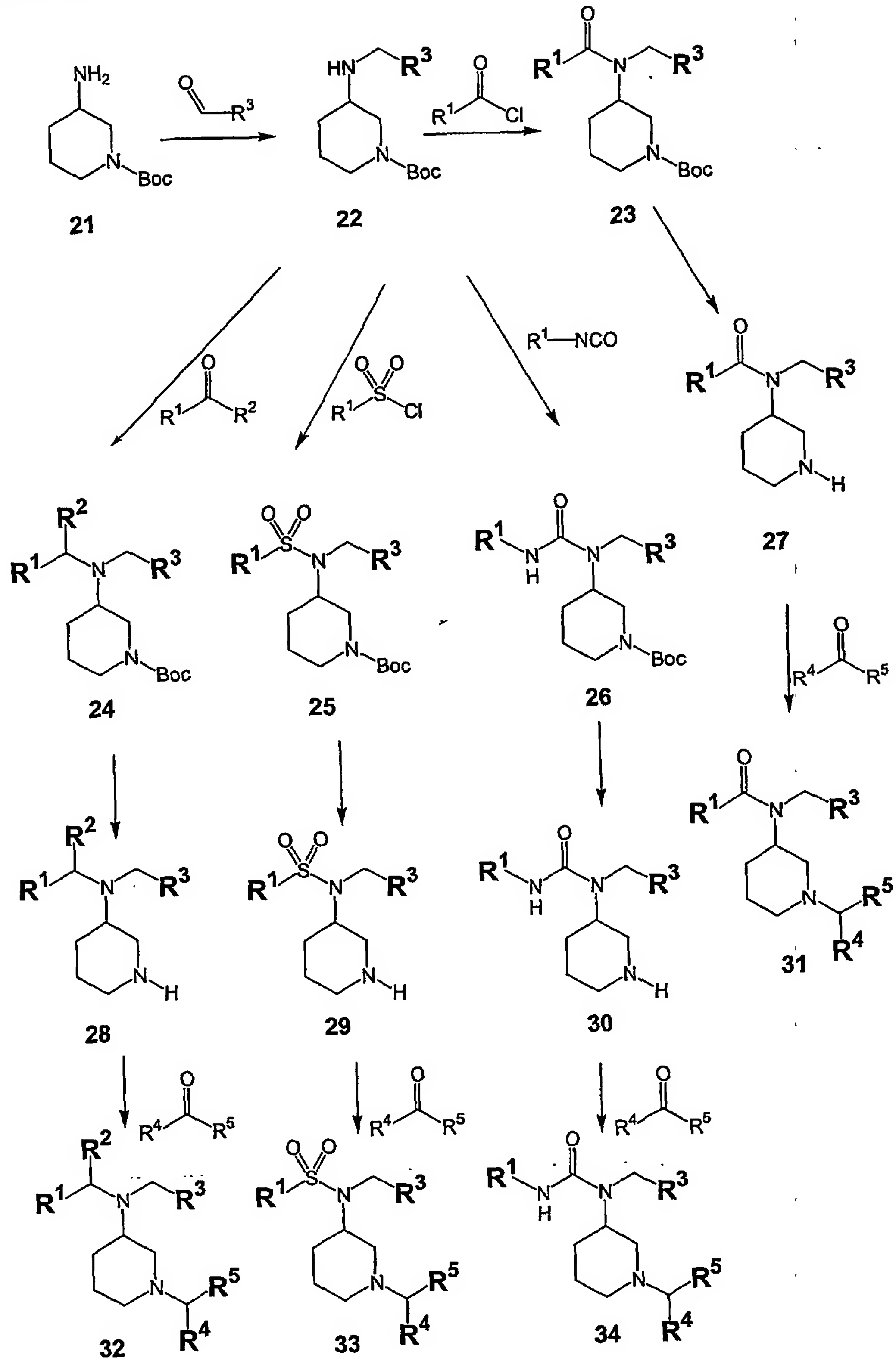


The N-Boc protected 4-amino-piperidine **7** (Scheme 2) can be prepared in a two step procedure starting by reacting 4-hydroxy-N-Boc-piperidine with methanesulfonylchloride in an inert solvent like DCM in the presence of a base like TEA to generate 4-mesyloxy-N-Boc-piperidine. The mesyloxy group is substituted with sodium azide followed by reduction of the azide functionality to the amino group to give **7**. The amine **7** is transformed to the secondary amine **8** via the typical procedure for the reductive amination described above. The synthesis of compounds **9, 10, 11** and **12** can also be performed via the typical procedures described above. Boc-deprotection is achieved either with hydrochloric acid in a solvent like diethylether or dioxane or with TFA in DCM. The second reductive amination step of the derivatives **13, 14, 15** and **16** to the fully derivatized final compounds **17, 18, 19** and **20** can be performed according to the typical procedure described above. Compounds **13, 14, 15** and **16** could also be transformed with acylating reagents like isocyanates, acid chlorides or sulfonyl chlorides to yield products with an urea-, amide- or sulfonamide functionality instead of the amine functionality at the ring nitrogen atom.

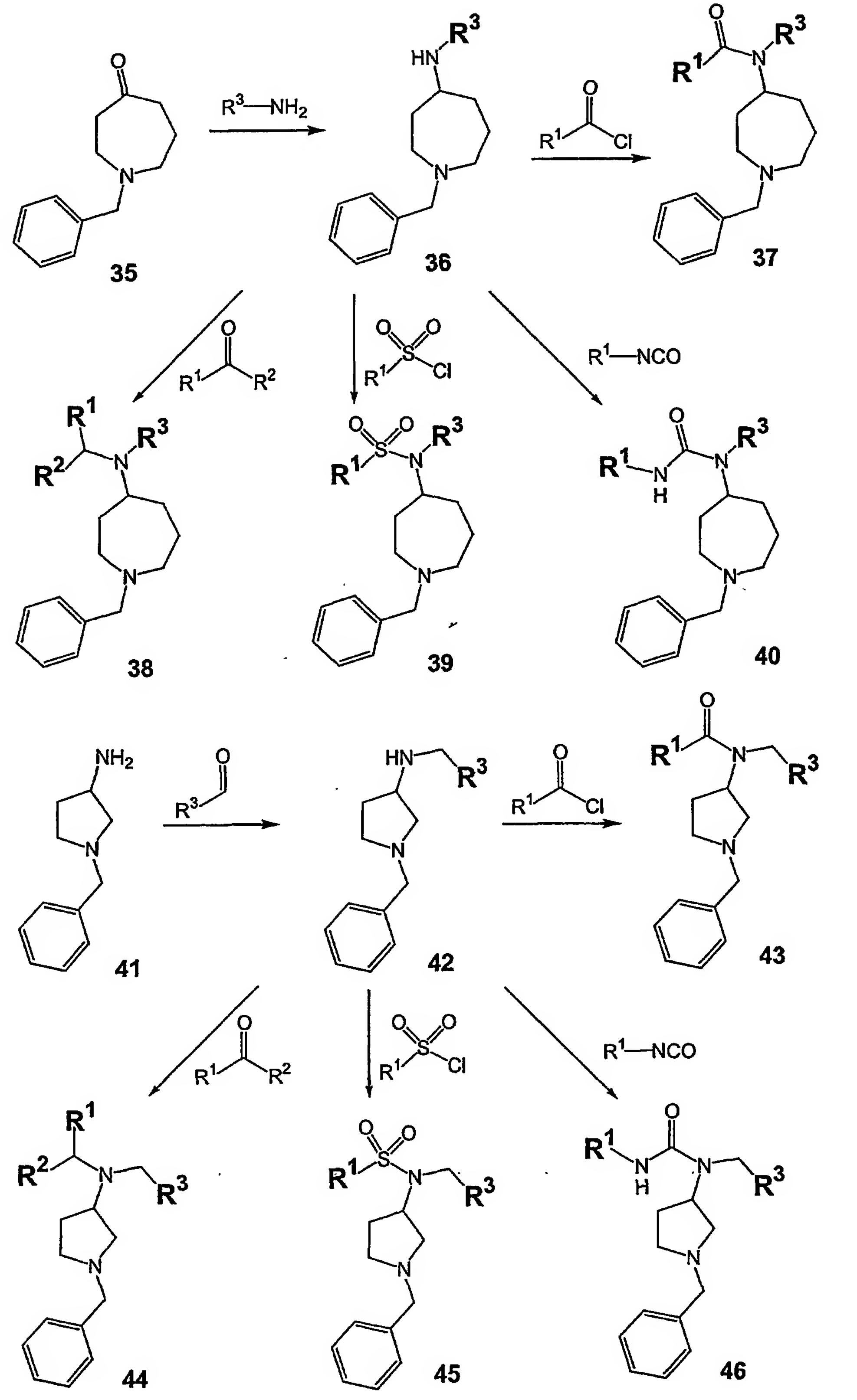
Compounds based on the 3-amino-piperidine template (see Scheme 3) can be prepared by using 3-amino-N-Boc-piperidine as starting material, which can be prepared as described for **7**. All other chemical transformations can be performed as described above in Scheme 2.

Compounds based on a 5- or 7-membered ring template (see Scheme 4) can be prepared according to the procedures described above.
The 7-membered ring **35** can be prepared by ring extension of 1-benzyl-4-piperidone with ethyl diazoacetate in presence of boron trifluoride etherate. Subsequent hydrolysis followed by decarboxylation upon heating a solution in 10% HCl gives the template **35**. Amine **36** is then obtained following the typical procedure for the second reductive amination.

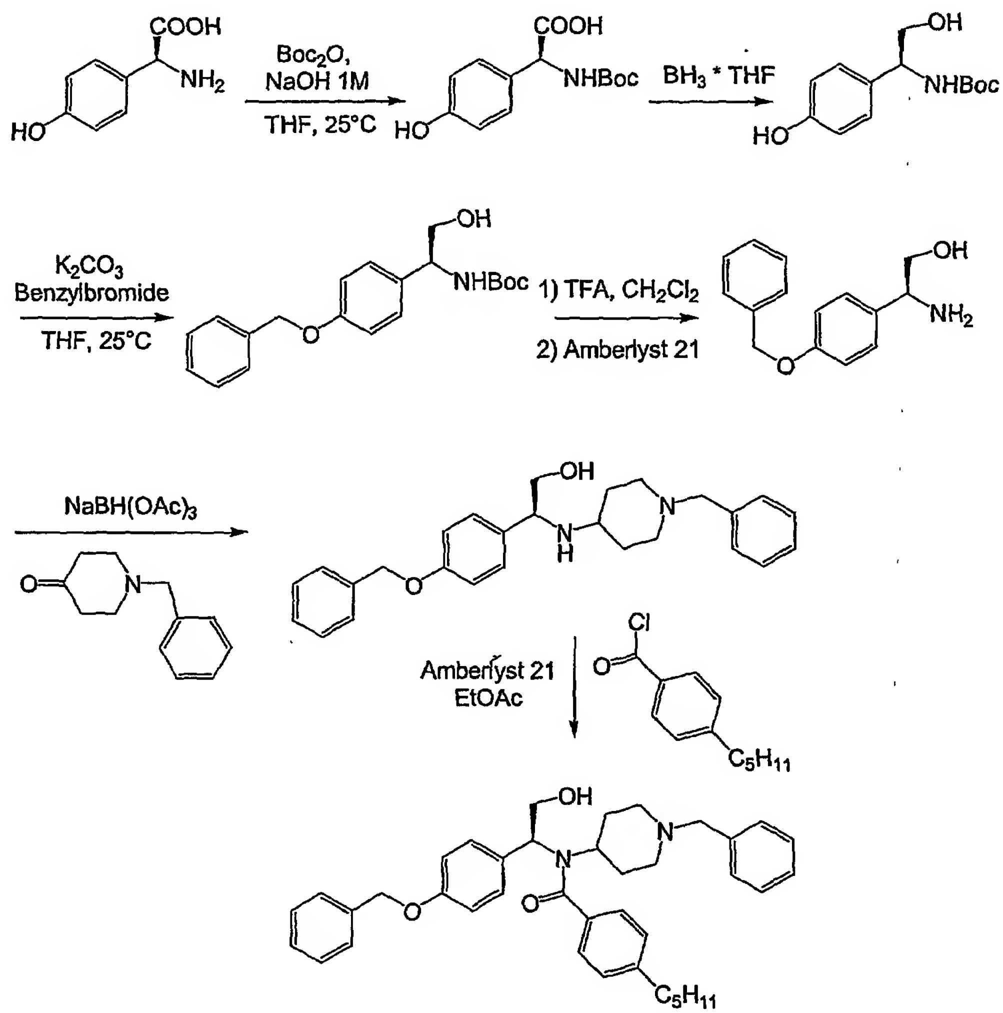
Scheme 3:



Scheme 4:



Scheme 5: Synthesis of "Hydroxymethyl-Analogues":



According to the synthesis of the example shown in Scheme 5, other derivatives can be prepared by variation of the starting materials.

All chemical transformations can be performed according to well known standard methodologies as described in the literature or as described in the typical procedures above.

The following examples illustrate the invention but do not limit the scope thereof. All temperatures are stated in °C.

List of abbreviations:

Boc or boc	tert.-butyloxycarbonyl
Cbz	benzyloxycarbonyl
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene(1,5-5)
DCM	dichloromethane
DMF	dimethylformamide
DMSO	dimethylsulfoxide
EtOAc	ethyl acetate
TEA	triethylamine
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography

General Procedures and Examples:

The following compounds were prepared according to the procedures described for the synthesis of compounds encompassed by the general formulae hereinbefore. All compounds were characterized by ^{1}H-NMR (300MHz) and occasionally by ^{13}C-NMR (75MHz) (Varian Oxford, 300MHz; chemical shifts are given in ppm relative to the solvent used; multiplicities: s = singlet, d = doublet, t = triplet; m = multiplet), by LC-MS (Waters Micromass; ZMD-platform with ESI-probe with Alliance 2790 HT; Column: 2x30mm, Gromsil ODS4, 3µm, 120A; Gradient: 0 – 100% acetonitrile in water, 6 min, with 0.05% formic acid, flow: 0.45ml/min; t_r is given in minutes, or Finnigan AQA/HP 1100; Column: Develosil C30 Aqua, 50x4.6mm, 5µm; Gradient: 5-95% acetonitrile in water, 1 min, with 0.03% TFA, flow:4.5 ml/min.), by TLC (TLC-plates from Merck, Silica gel 60 F_{254}) and occasionally by melting point.

a) General Procedures:

Typical procedure A) for the reductive amination:

The amine and the aldehyde (1.5 eq.) (which are used as starting materials, are known compounds or the synthesis is described above or below, respectively), are mixed in anhydrous methanol and stirred for 6 h. The mixture is then treated with sodium borohydride (1.5 eq.) and stirred for 2 h. Purified Amberlyst 15 or another suitable scavenger is added and the suspension is shaken for 12 h. The resin is then separated by filtration and washed with methanol. The secondary amine is removed from the resin by adding a 2 M methanolic ammonia solution. The resin is drained after 30 min and washed with methanol. The filtrate is evaporated to yield the pure secondary amine.

Typical procedure B) for the acylation:

To a solution of the amine in anhydrous ethyl acetate is added vacuum dried Amberlyst 21 or another suitable scavenger followed by the addition of the carboxylic acid chloride (1.5 eq.). After shaking the suspension for two hours, an aliquot of water is added in order to hydrolyze the excess of the carboxylic acid chloride and shaking is continued for 1 h. The resin is then removed by filtration, washed with ethyl acetate and the solution is evaporated to yield the pure amide.

Typical procedure C) for the second reductive amination:

The amine and the aldehyde (1.5 eq.) are mixed in anhydrous dichloromethane and sodium triacetoxyborohydride (1.3 eq.) is added. After stirring the solution for 48 h, methanol is added and the reaction mixture is treated in the same manner as described in procedure A).

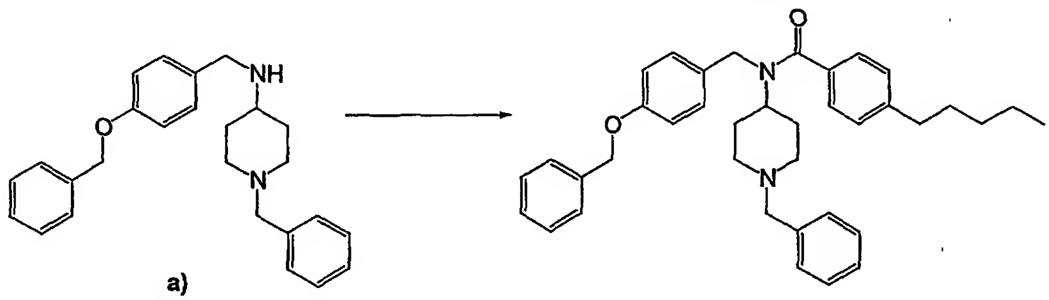
Typical procedure D) for the Suzuki coupling:

To a solution of bromide in toluene is added the boronic acid (1.1 eq.) in isopropanol and a 2M aqueous solution of potassium carbonate (5 eq.). The mixture is purged with nitrogen for 10 min and tetrakis (triphenylphosphine) palladium (0.03 eq.) is added. After heating under reflux for 6 h, water is added to the cooled reaction mixture and the product is extracted with ethyl acetate. The organic phase is washed with brine and dried over sodium sulfate. The solvent is evaporated to give the crude aldehyde, which is purified by flash chromatography (ethyl acetate/heptane gradient).

b) Examples:

Example 1:

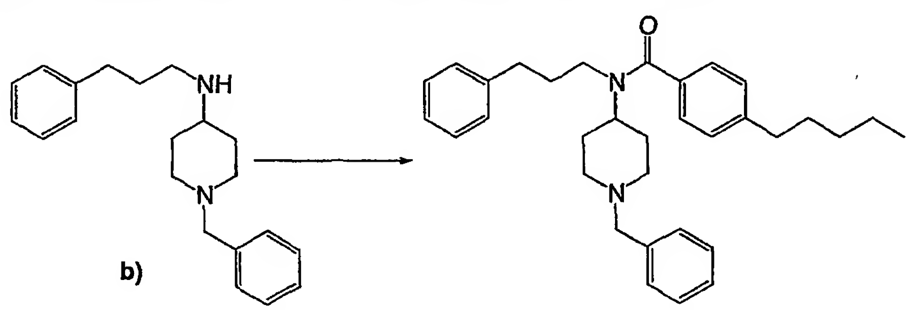
According to typical procedure B), the secondary amine **a)**, obtained via typical procedure A), is reacted with 4-pentylbenzoyl chloride to give



N-(4-Benzyloxybenzyl)-*N*-(1-benzylpiperidin-4-yl)-4-pentylbenzamide
LC-MS: t_R = 4.95; ES+: 561.7

Example 2:

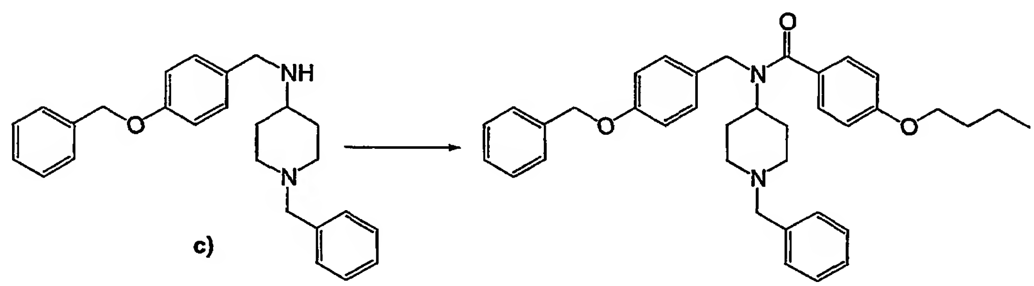
According to typical procedure B), the secondary amine **b)**, obtained via typical procedure A), is reacted with 4-pentylbenzoyl chloride to give



N-(1-Benzylpiperidin-4-yl)-4-pentyl-*N*-(3-phenylpropyl) benzamide
LC-MS: t_R = 4.82; ES+: 483.5

Example 3:

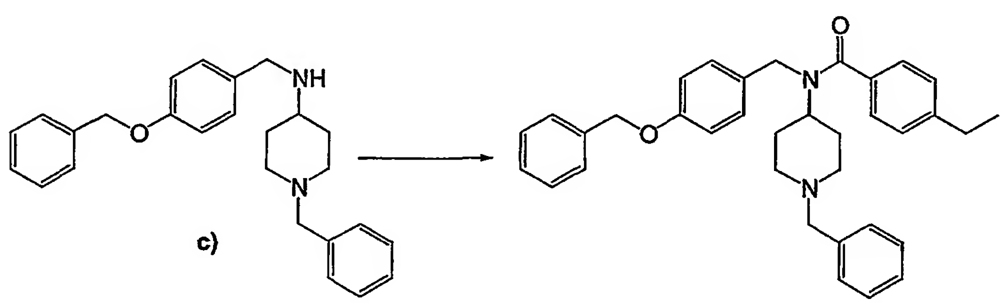
According to typical procedure B), the secondary amine **c)**, obtained via typical procedure A), is reacted with 4-butoxybenzoyl chloride to give



N-(4-Benzyloxybenzyl)-*N*-(1-benzylpiperidin-4-yl)-4-butoxybenzamide
LC-MS: t_R = 4.57; ES+:563.44

Example 4:

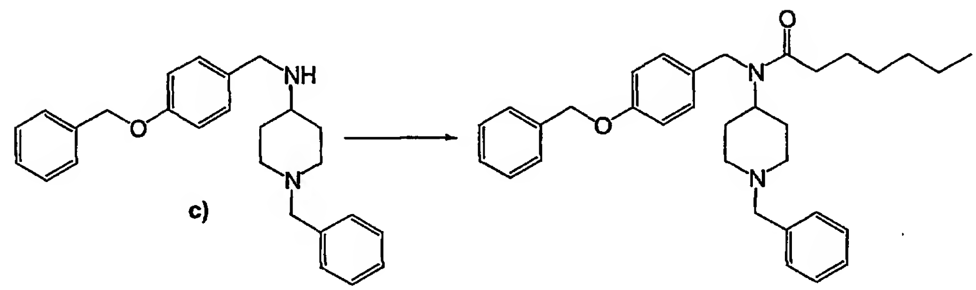
According to typical procedure B), the secondary amine **c)**, obtained via typical procedure A), is reacted with 4-ethylbenzoyl chloride to give



N-(4-Benzyloxybenzyl)-*N*-(1-benzylpiperidin-4-yl)-4-ethylbenzamide
LC-MS: t_R = 4.32; ES+:519.41

Example 5:

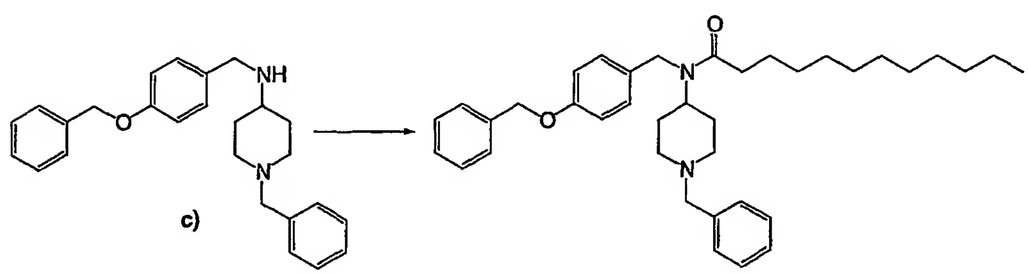
According to typical procedure B), the secondary amine **c)**, obtained via typical procedure A), is reacted with heptanoyl chloride to give



Heptanoic acid (4-benzyloxybenzyl)-(1-benzylpiperidin-4-yl) amide
LC-MS: t_R = 4.42; ES+: 499.39

Example 6:

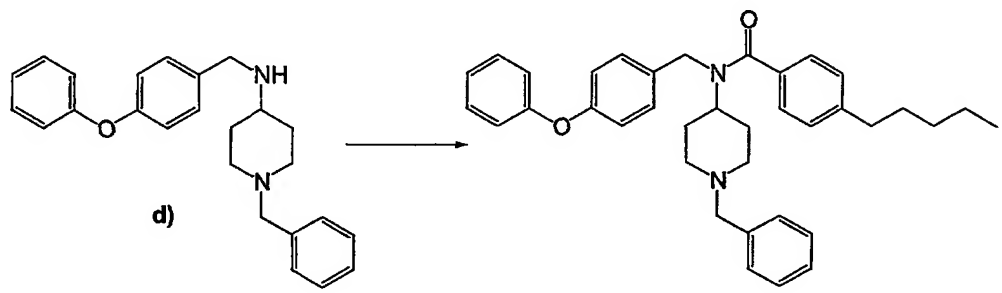
According to typical procedure B), the secondary amine **c)**, obtained via typical procedure A), is reacted with dodecanoyl chloride to give



Dodecanoic acid (4-benzyloxybenzyl)-(1-benzylpiperidin-4-yl) amide
LC-MS: t_R = 5.22; ES+: 569.56

Example 7:

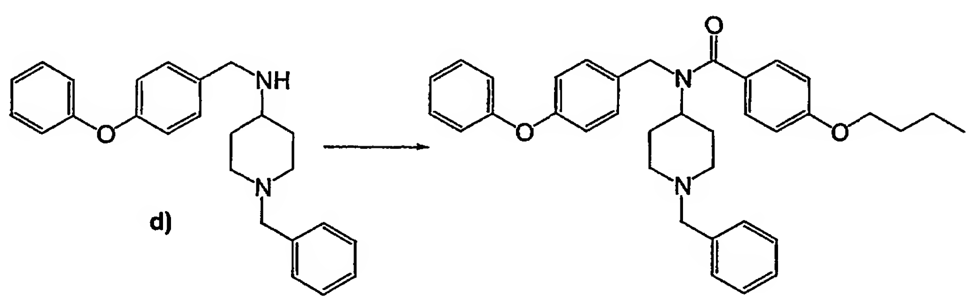
According to typical procedure B), the secondary amine **d)**, obtained via typical procedure A), is reacted with 4-pentylbenzoyl chloride to give



N-(1-Benzylpiperidin-4-yl)-4-pentyl-*N*-(4-phenoxybenzyl) benzamide
LC-MS: t_R = 4.80; ES+: 547.46

Example 8:

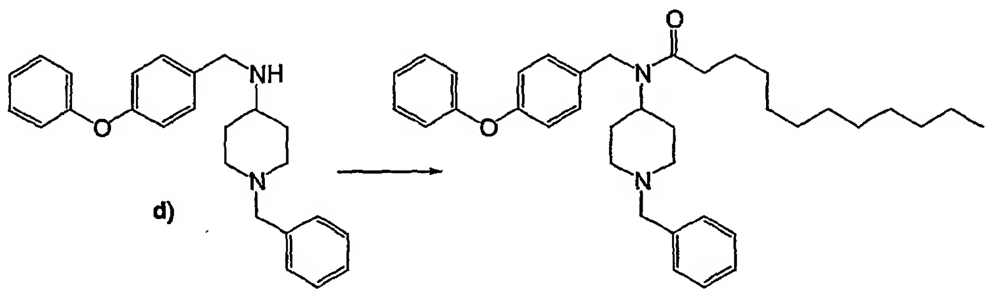
According to typical procedure B), the secondary amine **d)**, obtained via typical procedure A), is reacted with 4-butoxybenzoyl chloride to give



N-(1-Benzylpiperidin-4-yl)-4-butoxy-*N*-(4-phenoxybenzyl) benzamide
LC-MS: t_R = 4.60; ES+: 549.47

Example 9:

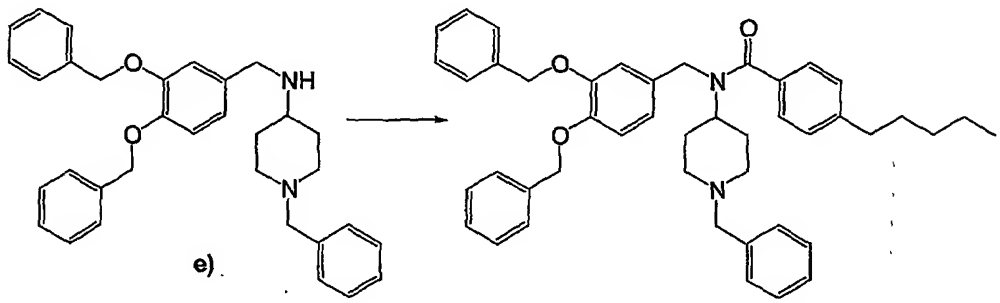
According to typical procedure B), the secondary amine **d)**, obtained via typical procedure A), is reacted with dodecanoyl chloride to give



Dodecanoic acid (1-benzylpiperidin-4-yl)-(4-phenoxybenzyl) amide
LC-MS: t_R = 5.16; ES+: 555.50

Example 10:

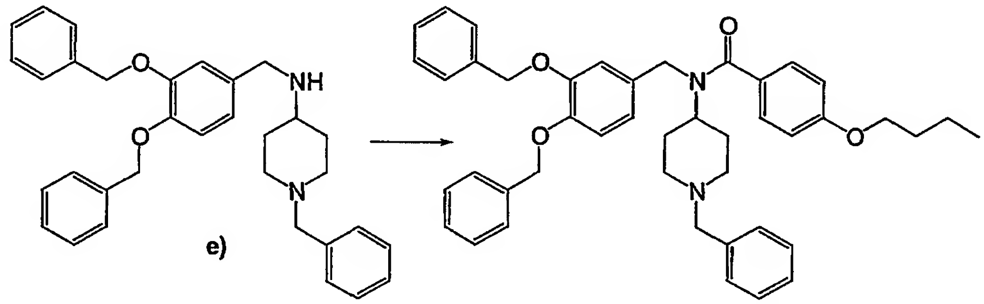
According to typical procedure B), the secondary amine **e)**, obtained via typical procedure A), is reacted with 4-pentylbenzoyl chloride to give



N-(1-Benzylpiperidin-4-yl)-*N*-(3,4-bis-benzyloxybenzyl)-4-pentylbenzamide
LC-MS: t_R = 5.05; ES+: 667.55

Example 11:

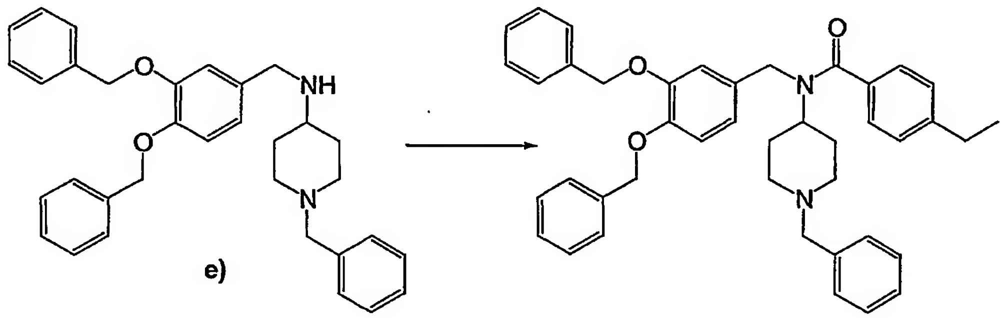
According to typical procedure B), the secondary amine **e)**, obtained via typical procedure A), is reacted with 4-butoxybenzoyl chloride to give



N-(1-Benzylpiperidin-4-yl)-*N*-(3,4-bis-benzyloxybenzyl)-4-butoxybenzamide
LC-MS: t_R = 4.83; ES+: 669.49

Example 12:

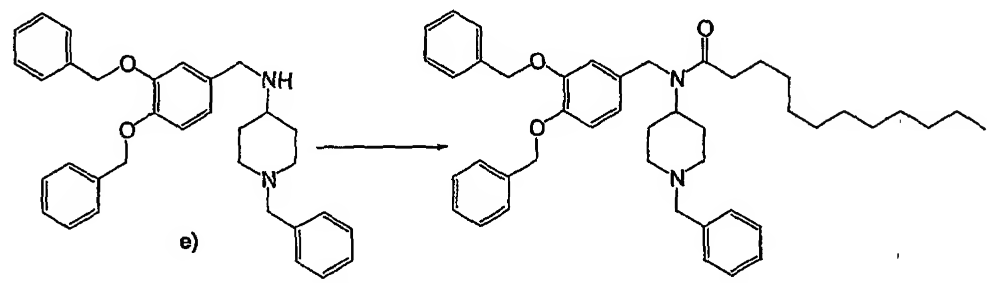
According to typical procedure B), the secondary amine **e)**, obtained via typical procedure A), is reacted with 4-ethylbenzoyl chloride to give



N-(1-Benzylpiperidin-4-yl)-*N*-(3,4-bis-benzyloxybenzyl)-4-ethylbenzamide
LC-MS: t_R = 4.59; ES+: 625.61

Example 13:

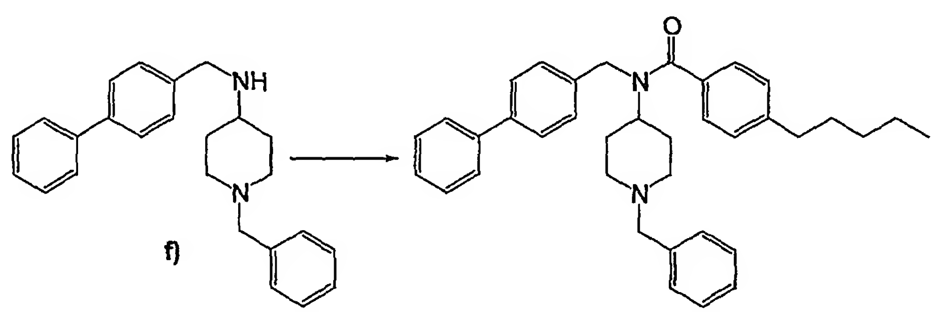
According to typical procedure B), the secondary amine **e)**, obtained via typical procedure A), is reacted with dodecanoyl chloride to give



Dodecanoic acid (1-benzylpiperidin-4-yl)-(3,4-bis-benzyloxybenzyl) amide
LC-MS: t_R = 5.49; ES+: 675.74

Example 14:

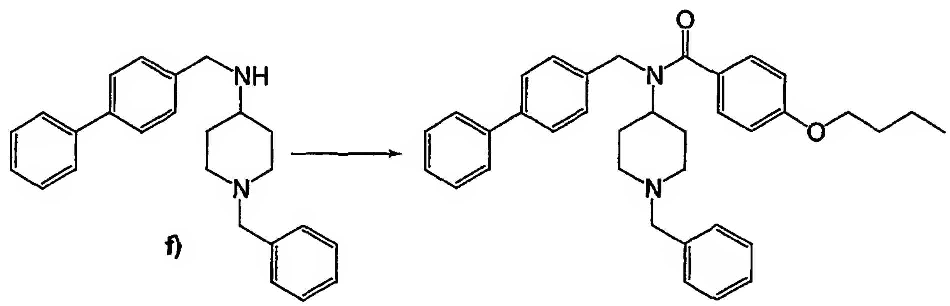
According to typical procedure B), the secondary amine **f)**, obtained via typical procedure A), is reacted with 4-pentylbenzoyl chloride to give



N-(1-Benzylpiperidin-4-yl)-*N*-biphenyl-4-ylmethyl-4-pentylbenzamide
LC-MS: t_R = 4.82; ES+: 531.46

Example 15:

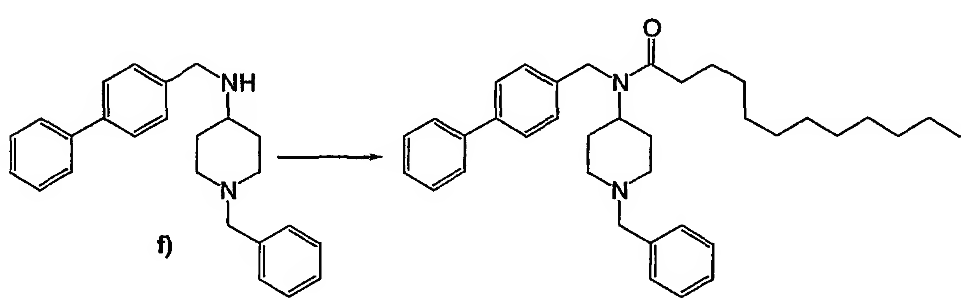
According to typical procedure B), the secondary amine **f)**, obtained via typical procedure A), is reacted with 4-butoxybenzoyl chloride to give



N-(1-Benzylpiperidin-4-yl)-*N*-biphenyl-4-ylmethyl-4-butoxybenzamide
LC-MS: t_R = 4.49; ES+: 533.43

Example 16:

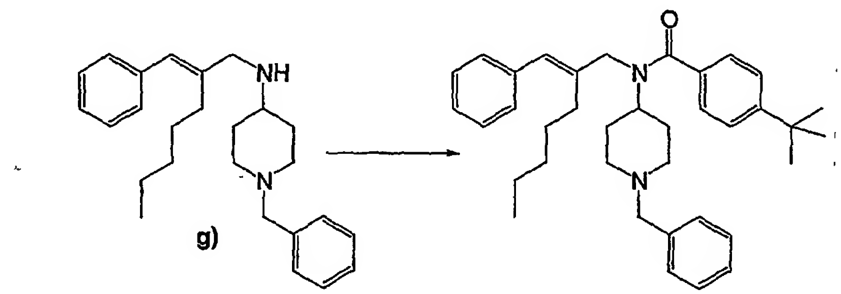
According to typical procedure B), the secondary amine **f)**, obtained via typical procedure A), is reacted with dodecanoyl chloride to give



Dodecanoic acid (1-benzylpiperidin-4-yl)-biphenyl-4-ylmethylamide
LC-MS: t_R = 5.22; ES+: 539.51

Example 17:

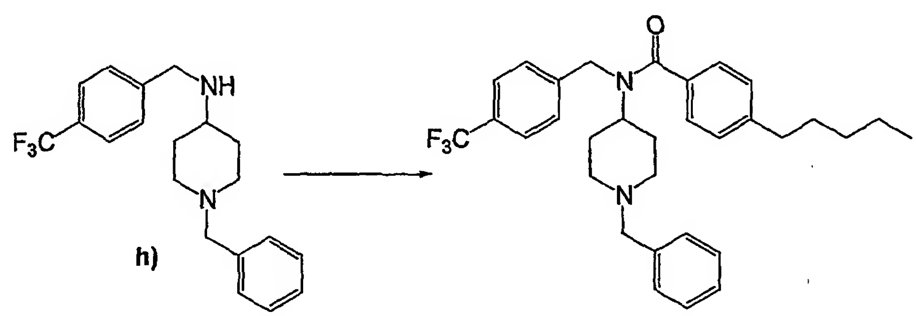
According to typical procedure B), the secondary amine **g)**, obtained via typical procedure A), is reacted with 4-*tert*-butylbenzoyl chloride to give



N-(1-Benzylpiperidin-4-yl)-4-*tert*-butyl-*N*-(2-pentyl-3-phenylallyl) benzamide
LC-MS: t_R = 4.93; ES+: 537.48

Example 18:

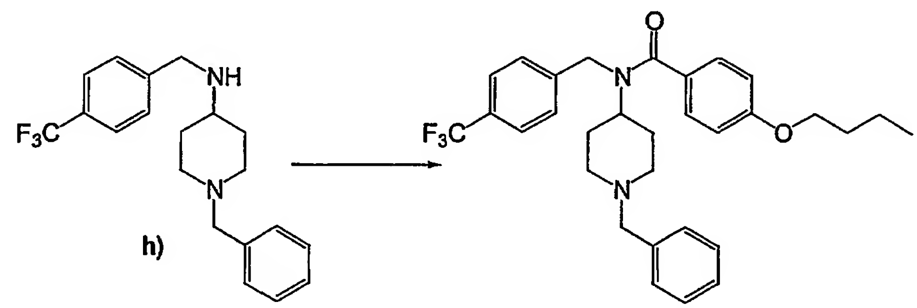
According to typical procedure B), the secondary amine **h)**, obtained via typical procedure A), is reacted with 4-pentylbenzoyl chloride to give



N-(1-Benzylpiperidin-4-yl)-4-pentyl-*N*-(4-trifluoromethylbenzyl) benzamide
LC-MS: t_R = 4.58; ES+: 523.43

Example 19:

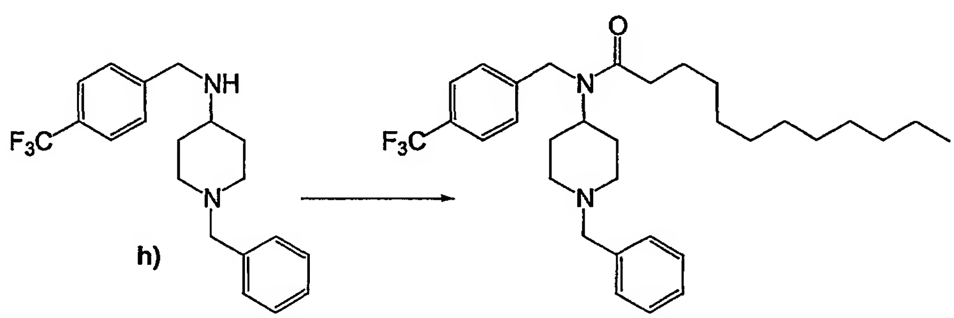
According to typical procedure B), the secondary amine **h)**, obtained via typical procedure A), is reacted with 4-butoxybenzoyl chloride to give



N-(1-Benzylpiperidin-4-yl)-4-butoxy-*N*-(4-trifluoromethylbenzyl) benzamide
LC-MS: t_R = 4.34; ES+: 525.48

Example 20:

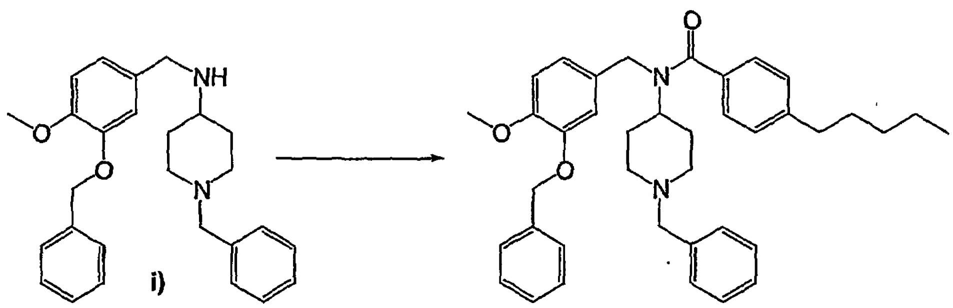
According to typical procedure B), the secondary amine **h)**, obtained via typical procedure A), is reacted with dodecanoyl chloride to give



Dodecanoic acid (1-benzylpiperidin-4-yl)-(4-trifluoromethylbenzyl) amide
LC-MS: t_R = 5.03; ES+: 531.43

Example 21

According to typical procedure B), the secondary amine **i)**, obtained via typical procedure A), is reacted with 4-pentylbenzoyl chloride to give

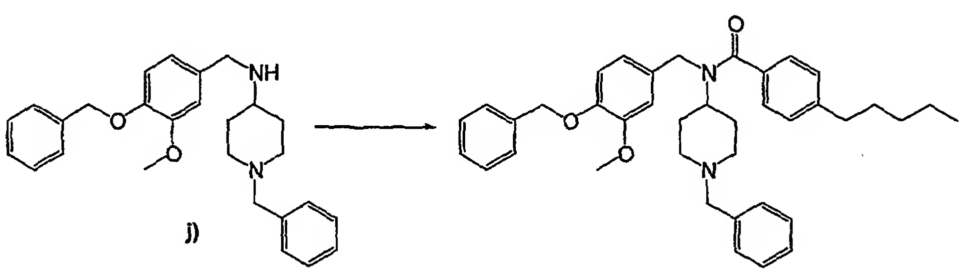


N-(3-Benzyloxy-4-methoxybenzyl)-*N*-(1-benzylpiperidin-4-yl)-4-pentylbenzamide

LC-MS: t_R = 4.62; ES+: 591.43

Example 22:

According to typical procedure B), the secondary amine **j)**, obtained via typical procedure A), is reacted with 4-pentylbenzoyl chloride to give

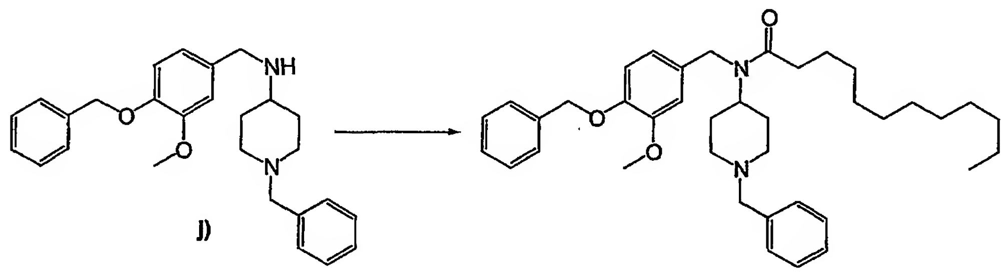


N-(4-Benzyloxy-3-methoxybenzyl)-*N*-(1-benzylpiperidin-4-yl)-4-pentylbenzamide

LC-MS: t_R = 4.70; ES+: 591.46

Example 23:

According to typical procedure B), the secondary amine j), obtained via typical procedure A), is reacted with dodecanoyl chloride to give



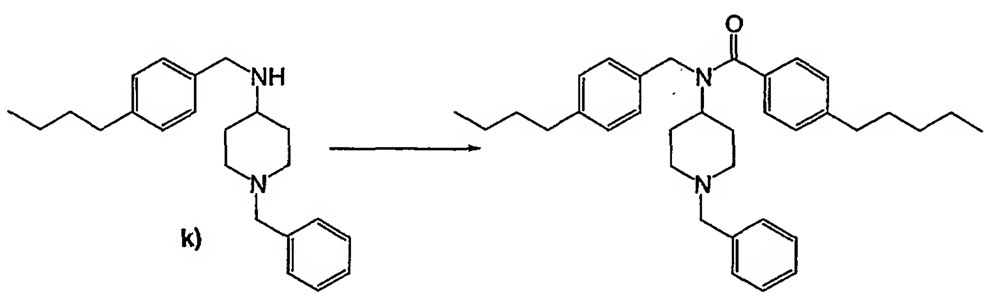
j)

Dodecanoic acid (4-benzyloxy-3-methoxybenzyl)-(1-benzylpiperidin-4-yl) amide

LC-MS: t_R = 5.12; ES+: 599.71

Example 24:

According to typical procedure B), the secondary amine k), obtained via typical procedure A), is reacted with 4-pentylbenzoyl chloride to give



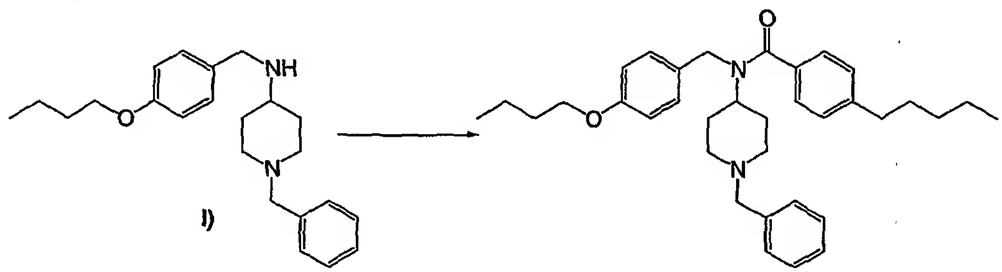
k)

N-(1-Benzylpiperidin-4-yl)-*N*-(4-butylbenzyl)-4-pentylbenzamide

LC-MS: t_R = 5.02; ES+: 511.56

Example 25:

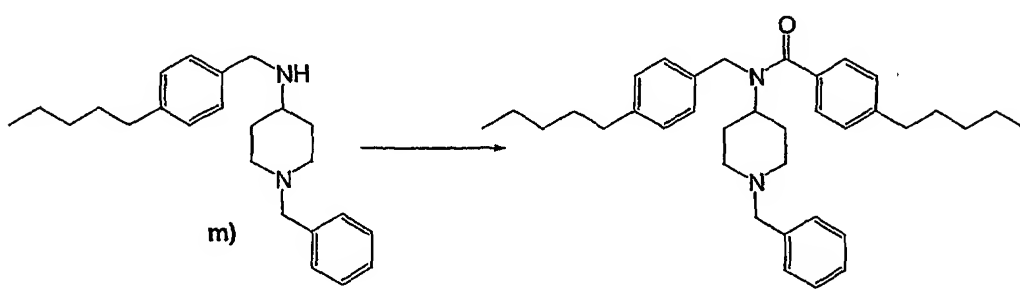
According to typical procedure B), the secondary amine **l)**, obtained via typical procedure A), is reacted with 4-pentylbenzoyl chloride to give



N-(1-Benzylpiperidin-4-yl)-*N*-(4-butoxybenzyl)-4-pentylbenzamide
LC-MS: t_R = 4.92; ES+: 527.58

Example 26:

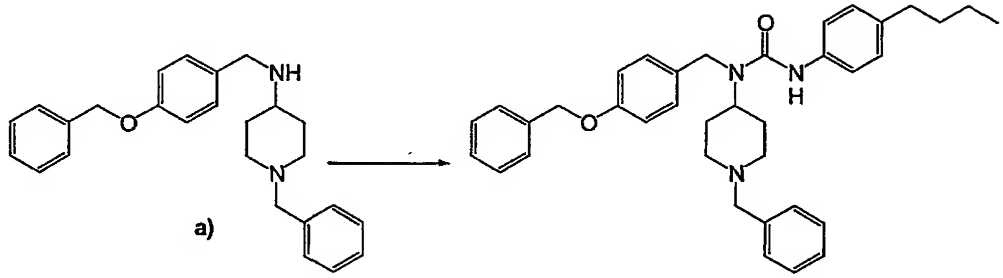
According to typical procedure B), the secondary amine **m)**, obtained via typical procedure A), is reacted with 4-pentylbenzoyl chloride to give



N-(1-Benzylpiperidin-4-yl)-4-pentyl-*N*-(4-pentylbenzyl) benzamide
LC-MS: t_R = 5.14; ES+: 525.60

Example 27:

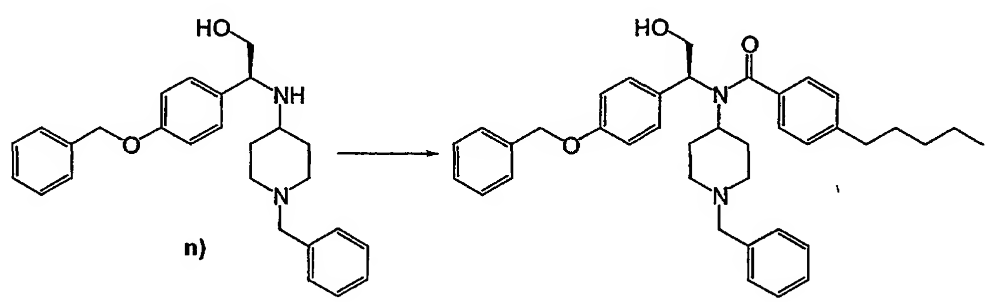
According to typical procedure B), the secondary amine **a)**, obtained via typical procedure A), is reacted with 4-butylphenylisocyanate to give



1-(4-Benzyloxybenzyl)-1-(1-benzylpiperidin-4-yl)-3-(4-butylphenyl) urea
LC-MS: t_R = 4.70; ES+: 562.53

Example 28:

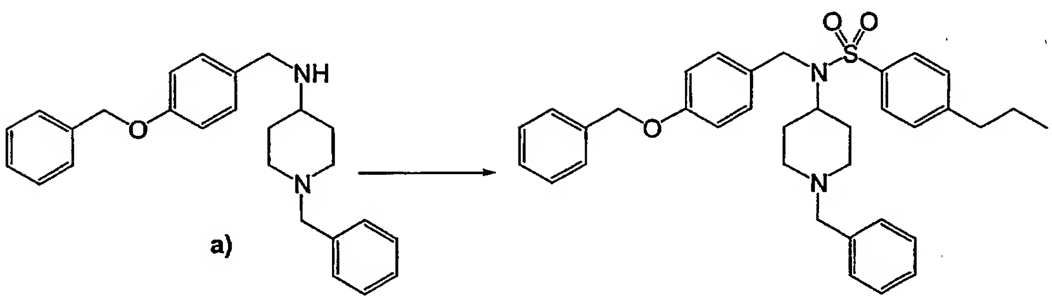
According to typical procedure B), the secondary amine **n)**, which is prepared as indicated in scheme 4, is reacted with 4-pentylbenzoyl chloride to give



N-[(*1S*)-1-(4-Benzyloxyphenyl)-2-hydroxyethyl]-*N*-(1-benzylpiperidin-4-yl)-4-pentylbenzamide
LC-MS: t_R = 4.47; ES+: 591.61

Example 29:

According to typical procedure B), the secondary amine **a)**, obtained via typical procedure A), is reacted with 4-propylphenylsulfonyl chloride to give



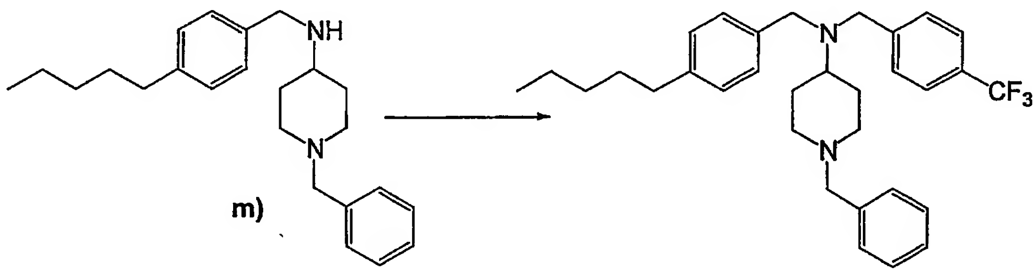
a)

N-(4-Benzyloxybenzyl)-*N*-(1-benzylpiperidin-4-yl)-4-propyl benzenesulfonamide

LC-MS: t_R = 4.63; ES+: 569.56

Example 30:

According to typical procedure C), the secondary amine **m)**, obtained via typical procedure A), is reacted with 4-trifluoromethylbenzaldehyde to give



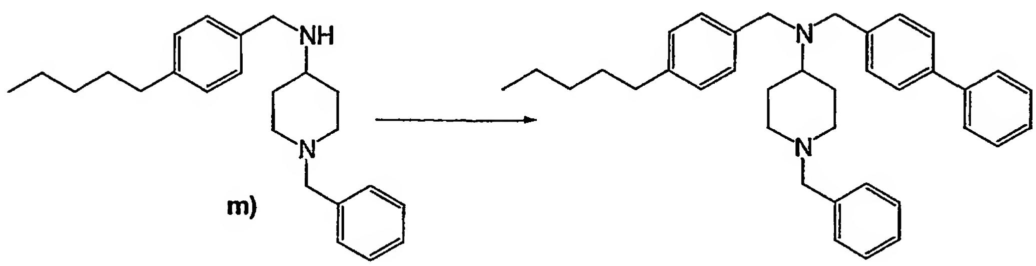
m)

(1-Benzylpiperidin-4-yl)-(4-pentylbenzyl)-(4-trifluoromethylbenzyl) amine

LC-MS: t_R = 4.91; ES+: 509.60

Example 31:

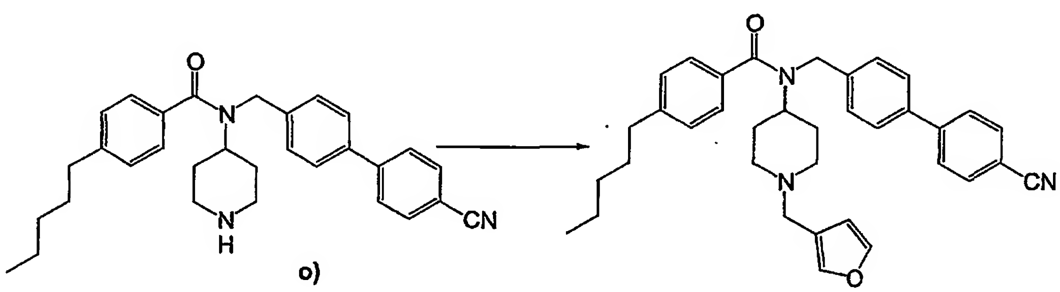
According to typical procedure C), the secondary amine **m)**, obtained via typical procedure A), is reacted with biphenyl-4-carbaldehyde to give



(1-Benzylpiperidin-4-yl)-biphenyl-4-ylmethyl-(4-pentylbenzyl) amine
LC-MS: t_R = 4.84; ES+: 517.55

Example 32:

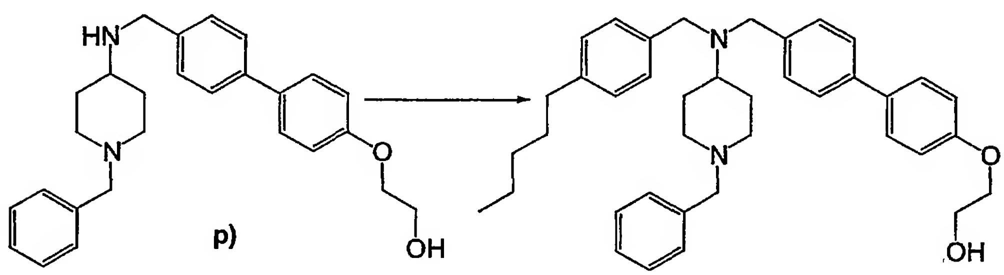
According to typical procedure C), the secondary amine **o)**, obtained via typical procedures A) and B), is reacted with furan-3-carbaldehyde to give



N-(4'-Cyanobiphenyl-4-ylmethyl)-*N*-(1-furan-3-ylmethylpiperidin-4-yl)-4-pentylbenzamide
LC-MS: t_R = 1.05 ; ES+: 546.19

Example 33:

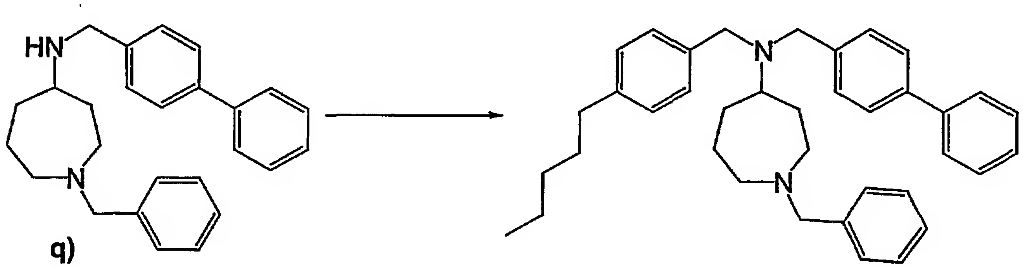
According to typical procedure C), the secondary amine **p)**, obtained via typical procedure A), is reacted with 4-pentylbenzaldehyde to give



2-(4'-{[(1-Benzylpiperidin-4-yl)-(4-pentylbenzyl)-amino]methyl}biphenyl-4-yloxy)ethanol
LC-MS: t_R = 4.32 ; ES+:577.49

Example 34:

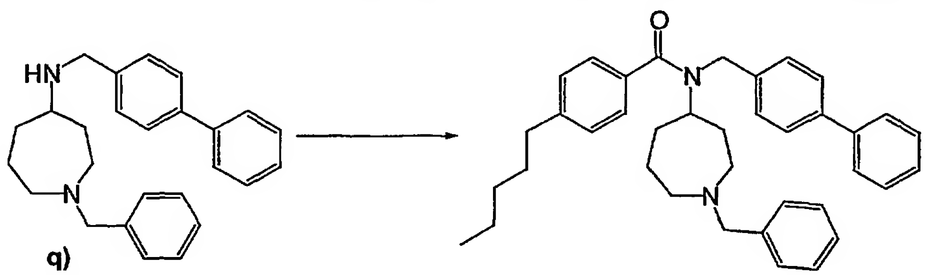
According to typical procedure C), the secondary amine **q)**, which is prepared as indicated in Scheme 4, is reacted with 4-pentylbenzaldehyde to give



(rac.)-(1-Benzylazepan-4-yl)biphenyl-4-ylmethyl-(4-pentylbenzyl) amine
LC-MS: t_R = 4.41 ; ES+:531.53

Example 35:

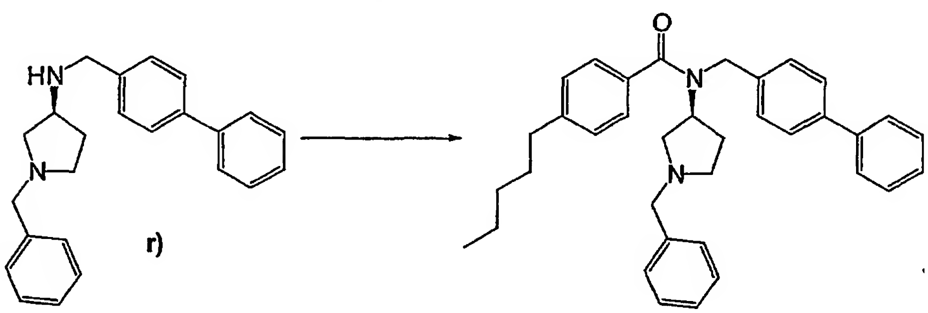
According to typical procedure B), the secondary amine **q)**, which is prepared as indicated in Scheme 4, is reacted with 4-pentylbenzoyl chloride to give



(rac.)-N-(1-Benzylazepan-4-yl)-N-biphenyl-4-ylmethyl-4-pentyl benzamide
LC-MS: t_R = 4.94; ES+:545.42

Example 36:

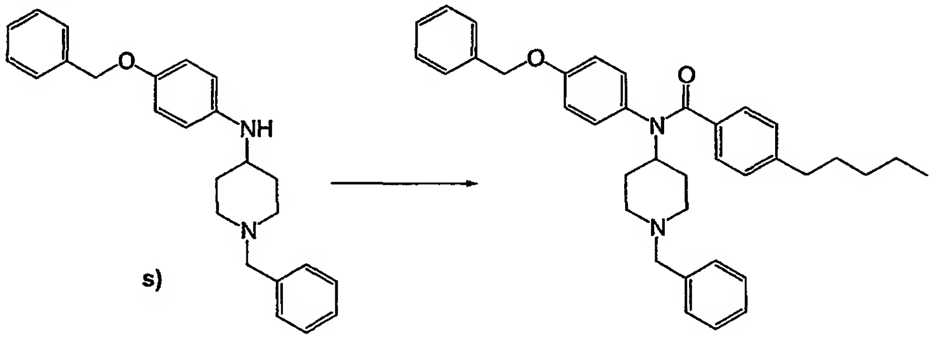
According to typical procedure B), the secondary amine **r)**, obtained via typical procedure A), is reacted with 4-pentylbenzoyl chloride to give



N-((3*S*)-1-Benzylpyrrolidin-3-yl)-*N*-biphenyl-4-ylmethyl-4-pentylbenzamide
LC-MS: t_R = 5.08 ; ES+:517.44

Example 37:

According to typical procedure B), the secondary amine **s)**, obtained via typical procedure C), is reacted with 4-pentylbenzoyl chloride to give



N-(4-Benzyloxyphenyl)-*N*-(1-benzylpiperidin-4-yl)-4-pentylbenzamide
LC-MS: t_R = 4.57 ; ES+: 547.34

Additional Examples:

Example Nr	Compound	LC-MS	Synthesis according to example	IC_{50} (nM) on plasmepsin II
38	N-(1-Cyclohex-1-enylmethyl-piperidin-4-yl)-N-(3',4'-dimethoxy-biphenyl-4-ylmethyl)-4-pentylbenzamide	t_R=0.82[a] ES+: 595.26	32	19
39	N-[1-(3-Methylbutyl) piperidin-4-yl]-4-pentyl-N-(4-pyridin-3-yl-benzyl) benzamide	t_R=3.78 ES+: 512.56	32	20
40	N-(4'-Cyanobiphenyl-4-ylmethyl)-N-(1-cyclohex-1-enylmethyl-piperidin-4-yl)-4-pentylbenzamide	t_R=1.09[a] ES+: 560.25	32	25
41	N-(3',4'-Dimethoxybiphenyl-4-ylmethyl)-4-pentyl-N-(1-pyridin-4-ylmethylpiperidin-4-yl) benzamide	t_R=0.95[a] ES+: 592.24	32	25

42	N-(4'-Cyano-biphenyl-4-ylmethyl)-4-pentyl-N-(1-pyridin-4-ylmethyl-piperidin-4-yl) benzamide	t_R=0.71[a] ES+: 557.20	32	28
43	N-(3',4'-Dimethoxybiphenyl-4-ylmethyl)-N-(1-furan-3-ylmethyl-piperidin-4-yl)-4-pentylbenzamide	t_R=0.79[a] ES+: 581.21	32	31
44	N-[4'-(2-Hydroxyethoxy)-biphenyl-4-ylmethyl]-4-pentyl-N-(1-pyridin-4-ylmethylpiperidin-4-yl) benzamide	t_R=0.89[a] ES+: 592.24	32	39
45	4-Pentyl-N-(4-pyridin-3-yl-benzyl)-N-(1-thiophen-3-ylmethyl-piperidin-4-yl) benzamide	t_R=3.73 ES+: 538.33	32	42
46	N-(3',4'-Dimethoxybiphenyl-4-ylmethyl)-4-pentyl-N-(1-pyridin-3-ylmethylpiperidin-4-yl) benzamide	t_R=0.96[a] ES+: 592.26	32	45
47	N-(1-Cyclohexylmethyl-piperidin-4-yl)-4-pentyl-N-(4-pyridin-3-yl-benzyl) benzamide	t_R=3.90 ES+: 538.38	32	46
48	N-(1-Benzylpiperidin-4-yl)-N-(3',4'-dimethoxybiphenyl-4-ylmethyl)-4-pentylbenzamide	t_R=4.58 ES+: 591.57	14	48
49	N-(4-Benzo[1,3]dioxol-5-yl-benzyl)-N-(1-furan-3-ylmethyl-piperidin-4-yl)-4-pentylbenzamide	t_R=4.72 ES+: 565.37	32	52
50	N-(4-Benzo[1,3]dioxol-5-yl-benzyl)-4-pentyl-N-(1-pyridin-4-ylmethylpiperidin-4-yl) benzamide	t_R=4.59 ES+: 576.60	32	54
51	N-(1-Furan-3-ylmethylpiperidin-4-yl)-N-[4'-(2-hydroxyethoxy) biphenyl-4-ylmethyl]-4-pentylbenzamide	t_R=0.98[a] ES+: 581.22	32	57

52	N-(4-Benzo[1,3]dioxol-5-yl-benzyl)-N-(1-benzylpiperidin-4-yl)-4-pentylbenzamide	t_R=4.87 ES+: 575.61	14	58
53	N-(1-Benzylpiperidin-4-yl)-N-(2'-fluorobiphenyl-4-ylmethyl)-4-pentylbenzamide	t_R=4.65 ES+: 549.47	14	61
54	N-(1-Furan-3-ylmethylpiperidin-4-yl)-4-pentyl-N-(4-pyridin-3-yl-benzyl) benzamide	t_R=3.96 ES+: 522.42	32	64
55	N-(4'-Cyanobiphenyl-4-ylmethyl)-4-pentyl-N-(1-pyridin-3-ylmethyl-piperidin-4-yl) benzamide	t_R=0.72 [a] ES+: 557.18	32	68
56	N-Biphenyl-4-ylmethyl-N-[1-(4-methoxybenzyl) piperidin-4-yl]-4-pentylbenzamide	t_R=5.02 ES+: 561.57	32	71
57	N-(4-Benzo[1,3]dioxol-5-yl-benzyl)-N-(1-cyclohex-1-enylmethyl-piperidin-4-yl)-4-pentyl-benzamide	t_R=5.20 ES+: 579.55	32	75
58	N-(1-Benzyl-piperidin-4-yl)-N-[4-(4-fluoro-benzyloxy)-benzyl]-4-pentyl-benzamide	t_R=4.83 ES+: 579.71	1	79
59	N-(1-Benzyl-piperidin-4-yl)-N-(4'-cyano-biphenyl-4-ylmethyl)-4-pentyl-benzamide	t_R=4.69 ES+: 556.58	14	81
60	N-(2'-Fluorobiphenyl-4-ylmethyl)-N-(1-furan-3-ylmethylpiperidin-4-yl)-4-pentylbenzamide	t_R=4.77 ES+: 539.36	32	87
61	N-(1-Cyclohex-1-enylmethyl-piperidin-4-yl)-4-pentyl-N-(4-pyridin-3-yl-benzyl) benzamide	t_R=4.44 ES+: 536.44	32	89

62	N-(4-Benzo[1,3]dioxol-5-yl-benzyl)-N-[1-(4-hydroxybenzyl) piperidin-4-yl]-4-pentylbenzamide	t_R=4.89 ES+: 591.72	32	90
63	N-(2'-Fluorobiphenyl-4-ylmethyl)-4-pentyl-N-(1-pyridin-4-ylmethyl-piperidin-4-yl) benzamide	t_R=4.65 ES+: 550.40	32	95
64	4-Pentyl-N-(4-pyridin-3-yl-benzyl)-N-(1-pyridin-4-ylmethylpiperidin-4-yl) benzamide	t_R=3.72 ES+: 533.24	32	102
65	N-Biphenyl-4-ylmethyl-4-pentyl-N-(1-pyridin-3-ylmethylpiperidin-4-yl) benzamide	t_R=4.54 ES+: 532.46	32	103
66	N-(1-Benzylpiperidin-4-yl)-4-pentyl-N-(4-pyridin-4-ylbenzyl) benzamide	t_R=4.22 ES+: 532.48	14	104
67	N-[1-(4-Hydroxybenzyl) piperidin-4-yl]-4-pentyl-N-(4-pyridin-3-yl-benzyl) benzamide	t_R=4.00 ES+: 548.42	32	105
68	N-(1-Benzylpiperidin-4-yl)-N-(2'-chlorobiphenyl-4-ylmethyl)-4-pentylbenzamide	t_R=4.76 ES+: 565.60	14	120
69	N-(1-Cyclohex-1-enylmethyl-piperidin-4-yl)-N-(2'-fluoro-biphenyl-4-ylmethyl)-4-pentylbenzamide	t_R=5.30 ES+: 553.49	32	123
70	N-(1-Cyclohex-1-enylmethyl-piperidin-4-yl)-4-pentyl-N-(4-pyridin-2-ylbenzyl) benzamide	t_R=4.64 ES+: 536.49	32	125
71	N-Biphenyl-4-ylmethyl-N-(1-furan-3-ylmethyl-piperidin-4-yl)-4-pentylbenzamide	t_R=4.68 ES+: 521.40	32	127

72	N-[1-(5-Hydroxymethyl-furan-2-ylmethyl) piperidin-4-yl]-4-pentyl-N-(4-pyridin-3-ylbenzyl) benzamide	t_R=3.52 ES+: 552.20	32	128
73	N-(1-Cyclopropylmethylpiperidin-4-yl)-4-pentyl-N-(4-pyridin-3-yl-benzyl) benzamide	t_R=3.65 ES+: 496.36	32	128
74	N-(1-Benzylpiperidin-4-yl)-N-(3'-methylbiphenyl-4-ylmethyl)-4-pentylbenzamide	t_R=4.97 ES+: 545.42	14	140
75	N-(4-Benzyloxybenzyl)-N-((3S)-1-benzylpyrrolidin-3-yl)-4-pentyl-benzamide	t_R=5.00 ES+: 547.37	36	141
76	N-(2'-Fluorobiphenyl-4-ylmethyl)-N-[1-(4-hydroxybenzyl) piperidin-4-yl]-4-pentylbenzamide	t_R=4.95 ES+: 565.56	32	152
77	N-(1-Benzylpiperidin-4-yl)-N-(3-fluoro-4-trifluoromethylbenzyl)-4-pentylbenzamide	t_R=4.58 ES+: 541.30	1	153
78	N-(1-Furan-3-ylmethylpiperidin-4-yl)-4-pentyl-N-(4-pyridin-2-yl-benzyl) benzamide	t_R=4.24 ES+: 522.33	32	168
79	4-Pentyl-N-(4-pyridin-2-yl-benzyl)-N-(1-pyridin-4-ylmethylpiperidin-4-yl) benzamide	t_R=3.97 ES+: 533.49	32	176
80	N-(1-Benzylpiperidin-4-yl)-4-pentyl-N-(4-trifluoromethoxy-benzyl) benzamide	t_R=4.61 ES+: 539.46	1	187
81	N-Biphenyl-4-ylmethyl-N-[1-(4-hydroxybenzyl) piperidin-4-yl]-4-pentylbenzamide	t_R=4.68 ES+: 547.43	32	192

82	N-Biphenyl-4-ylmethyl-N-(1-cyclohex-1-enylmethylpiperidin-4-yl)-4-pentylbenzamide	t_R=5.11 ES+: 535.47	32	196
83	N-(1-Benzylpiperidin-4-yl)-N-(4-isopropoxybenzyl)-4-pentyl-benzamide	t_R=4.60 ES+: 513.35	1	204
84	N-(1-Benzylpiperidin-4-yl)-4-pentyl-N-(4-pyridin-2-yl-benzyl) benzamide	t_R=4.25 ES+: 518.45	14	209
85	N-(1-Benzofuran-2-ylmethyl-piperidin-4-yl)-4-pentyl-N-(4-pyridin-3-yl-benzyl) benzamide	t_R=3.99 ES+: 572.35	32	211
86	N-(1-Benzylpiperidin-4-yl)-N-naphthalen-2-ylmethyl-4-pentyl-benzamide	t_R=4.50 ES+: 505.17	1	248
87	N-(1-Benzylpiperidin-4-yl)-4-pentyl-N-(4-pyrimidin-5-ylbenzyl) benzamide	t_R=4.15 ES+: 533.40	14	250
88	(1-Benzylpiperidin-4-yl)-(3',4'-dimethoxybiphenyl-4-ylmethyl)-(4-pentyl-benzyl) amine	t_R=4.74 ES+: 577.40	33	255
89	N-(1-Benzylpiperidin-4-yl)-N-(4'-fluorobiphenyl-4-ylmethyl)-4-pentylbenzamide	t_R=4.77 ES+: 549.43	14	260
90	N-(4-Allyloxybenzyl)-N-(1-benzyl-piperidin-4-yl)-4-pentylbenzamide	t_R=4.56 ES+: 511.57	1	270
91	(4-Benzo[1,3]dioxol-5-yl-benzyl)-(1-benzylpiperidin-4-yl)-(4-pentyl-benzyl) amine	t_R=4.68 ES+: 561.53	33	275

92	N-(4-Benzyloxy-2-hydroxy-benzyl)-N-(1-benzylpiperidin-4-yl)-4-pentylbenzamide	t_R=4.76 ES+: 577.60	1	281
93	N-Benzo[1,3]dioxol-5-ylmethyl-N-(1-benzylpiperidin-4-yl)-4-pentyl-benzamide	t_R=4.50 ES+: 499.37	1	284
94	N-(1-Benzylpiperidin-4-yl)-N-(4-ethoxybenzyl)-4-pentylbenzamide	t_R=4.64 ES+: 499.42	1	284
95	4'-{[(1-Benzylpiperidin-4-yl)-(4-pentylbenzyl) amino] methyl}-biphenyl-4-carbonitrile	t_R=4.90 ES+: 542.33	14	294
96	N-Biphenyl-4-ylmethyl-4-pentyl-N-[1-(3-trifluoromethylbenzyl) piperidin-4-yl] benzamide	t_R=5.17 ES+: 599.67	32	319
97	N-(1-Benzylpiperidin-4-yl)-N-biphenyl-4-ylmethyl-4-hexyl-benzamide	t_R=4.82 ES+: 545.49	14	322
98	N-(1-Benzylpiperidin-4-yl)-N-(4-methoxybenzyl)-4-pentyl-benzamide	t_R=4.30 ES+: 485.34	1	322
99	N-Biphenyl-4-ylmethyl-N-[1-(2-hydroxybenzyl) piperidin-4-yl]-4-pentylbenzamide	t_R=4.80 ES+: 547.50	32	361
100	*trans*-4-Pentylcyclohexane carboxylic acid (1-benzylpiperidin-4-yl)-biphenyl-4-ylmethyl amide	t_R=4.91 ES+: 537.34	14	374
101	N-Biphenyl-4-ylmethyl-N-[1-(4-fluorobenzyl) piperidin-4-yl]-4-pentylbenzamide	t_R=4.98 ES+: 549.48	32	385

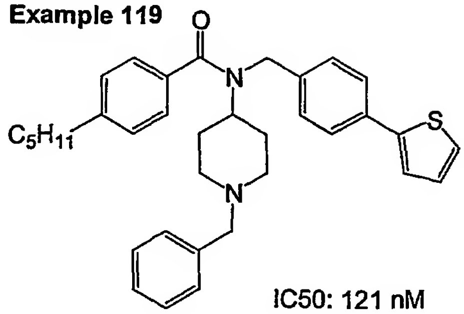
102	(1-Benzylpiperidin-4-yl)-[4-(4-fluorobenzyloxy) benzyl]-(4-pentylbenzyl) amine	t_R=4.71 ES+: 565.63	33	414
103	(4-Benzyloxybenzyl)-(1-benzyl-piperidin-4-yl)-(4-pentylbenzyl) amine	t_R=4.65 ES+: 547.56	33	431
104	N-Biphenyl-4-ylmethyl-4-pentyl-N-(1-phenethylpiperidin-4-yl) benzamide	t_R=4.91 ES+: 545.47	32	433
105	*(rac.)*-N-(4-Benzyloxybenzyl)-N-(1-benzylpiperidin-3-yl)-4-pentyl-benzamide	t_R=4.97 ES+: 561.46	1	458
106	N-(1-Benzylpiperidin-4-yl)-N-(4'-dimethylaminobiphenyl-4-ylmethyl)-4-pentylbenzamide	t_R=4.65 ES+: 574.54	14	461
107	(1-Benzylpiperidin-4-yl)-(4-pentyl-benzyl)-(4-pyrimidin-5-ylbenzyl) amine	t_R=4.36 ES+: 519.38	14	618
108	(1-Benzylpiperidin-4-yl)-(4-pentyl-benzyl)-(3'-trifluoromethyl-biphenyl-4-ylmethyl) amine	t_R=5.83 ES+: 585.43	14	634
109	(1-Benzylpiperidin-4-yl)-(2'-fluoro-biphenyl-4-ylmethyl)-(4-pentyl-benzyl) amine	t_R=4.96 ES+: 535.41	14	656
110	N-Biphenyl-4-ylmethyl-4-pentyl-N-[1-(4-trifluoromethoxybenzyl) piperidin-4-yl] benzamide	t_R=5.19 ES+: 615.63	32	692
111	N-[(*1S*)-2-(4-Benzyloxyphenyl)-1-hydroxymethylethyl]-N-(1-benzyl-piperidin-4-yl)-4-pentylbenzamide	t_R=4.32 ES+: 605.52	28	749

112	N-(4-Benzyloxybenzyl)-4-pentyl-N-(1-phenethylpiperidin-4-yl) benzamide	t_R=4.99 ES+: 575.49	32	761
113	N-(1-Benzylpiperidin-4-yl)-4-pentyl-N-(3'-trifluoromethoxy-biphenyl-4-ylmethyl) benzamide	t_R=5.11 ES+: 615.52	14	816
114	N-(4-Benzyloxybenzyl)-N-((3*R*)-1-benzylpyrrolidin-3-yl)-4-pentyl-benzamide	t_R=4.96 ES+: 547.42	36	817
115	N-(1-Benzylpiperidin-4-yl)-N-(4-dibutylaminobenzyl)-4-pentyl-benzamide	t_R=4.92 ES+: 582.74	1	839
116	N-(1-Benzylpiperidin-4-yl)-N-(4-hydroxybenzyl)-4-pentyl-benzamide	t_R=4.32 ES+: 471.42	1	882
117	N-(1-Benzylpiperidin-4-yl)-4-pentyl-N-(2-pentyl-3-phenylallyl) benzamide	t_R=5.21 ES+: 551.62	1	933
118	4-Pentylbicyclo[2.2.2]octane-1-carboxylic acid (1-benzylpiperidin-4-yl)-biphenyl-4-ylmethylamide	t_R=5.13 ES+: 563.67	1	942

[a] LC-MS measured on the Finningan AQA/HP system.

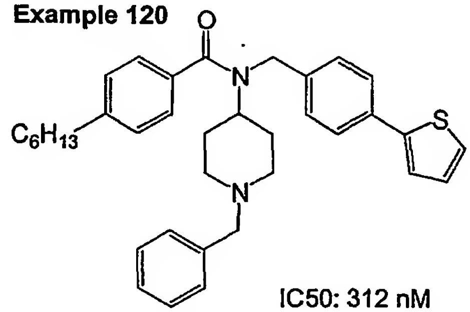
Further Examples:

Example 119



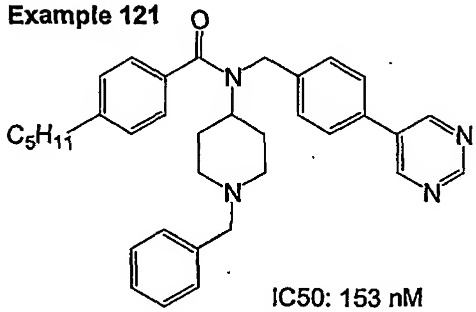
IC50: 121 nM

Example 120



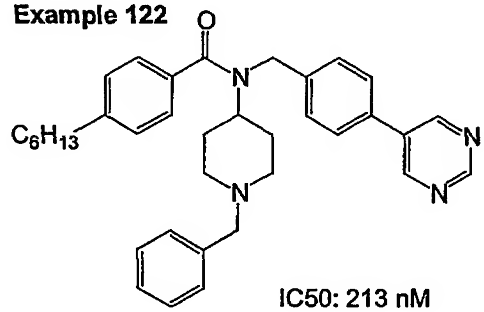
IC50: 312 nM

Example 121



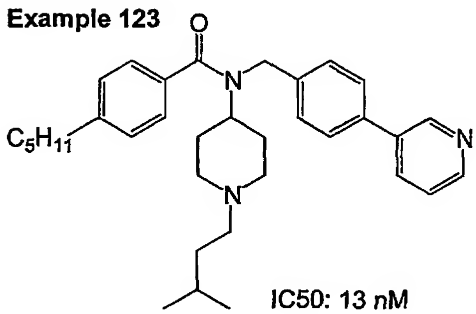
IC50: 153 nM

Example 122



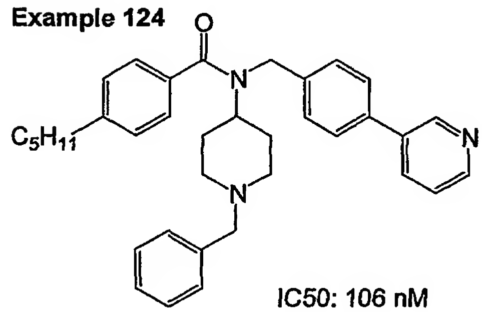
IC50: 213 nM

Example 123



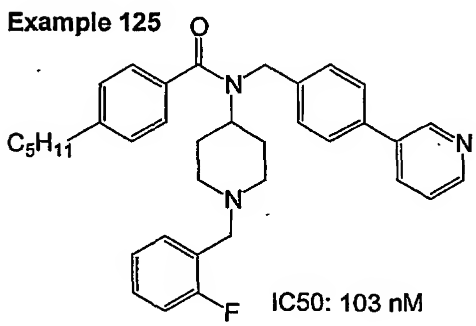
IC50: 13 nM

Example 124



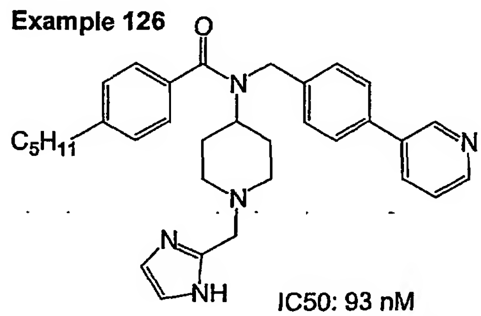
IC50: 106 nM

Example 125



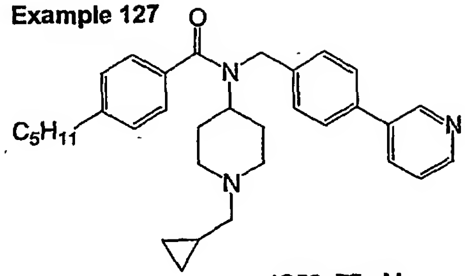
IC50: 103 nM

Example 126



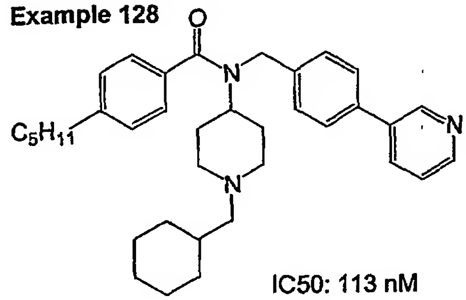
IC50: 93 nM

Example 127



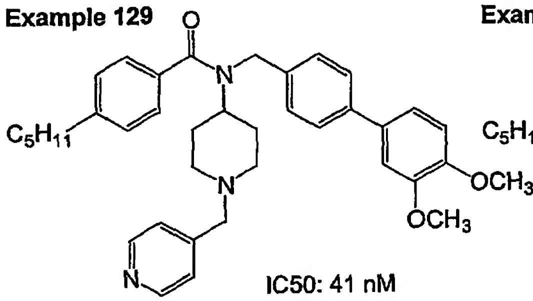
IC50: 77 nM

Example 128



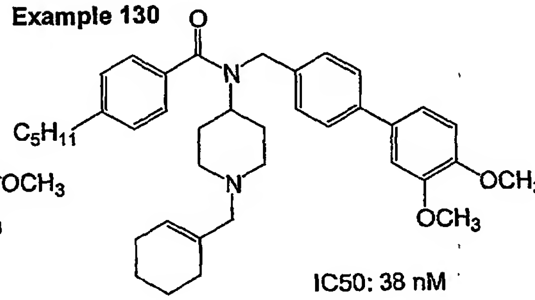
IC50: 113 nM

Example 129



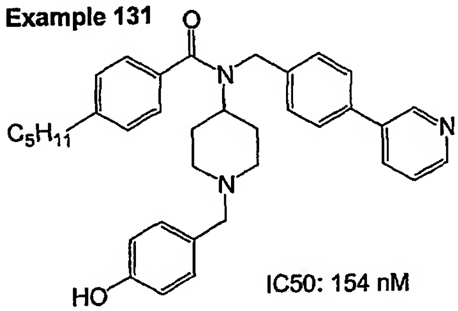
IC50: 41 nM

Example 130



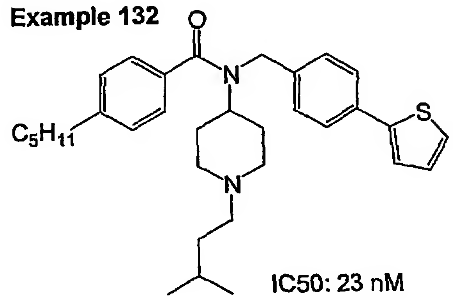
IC50: 38 nM

Example 131



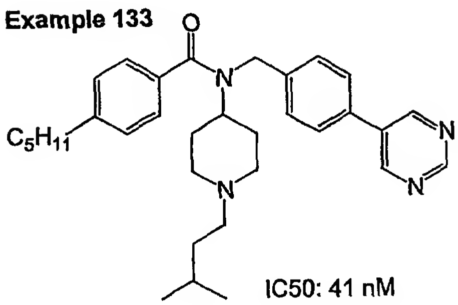
IC50: 154 nM

Example 132



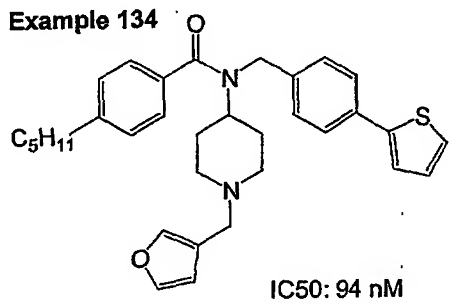
IC50: 23 nM

Example 133



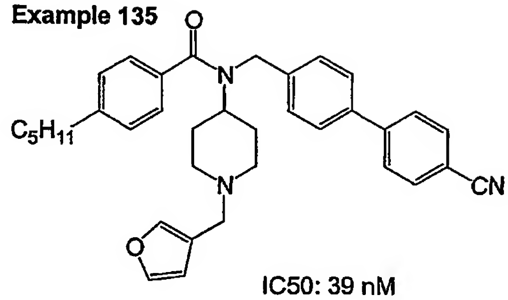
IC50: 41 nM

Example 134



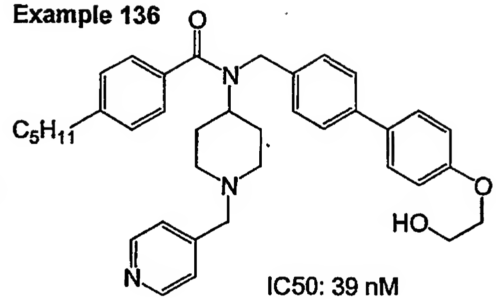
IC50: 94 nM

Example 135



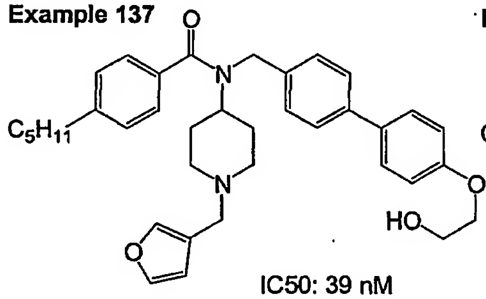
IC50: 39 nM

Example 136



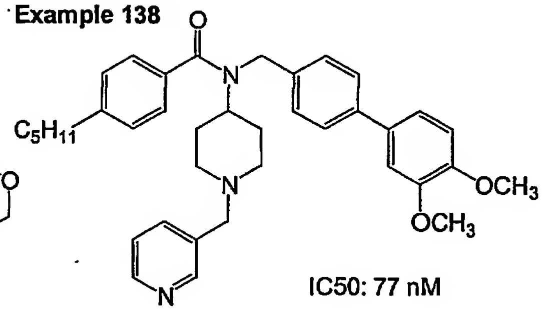
IC50: 39 nM

Example 137



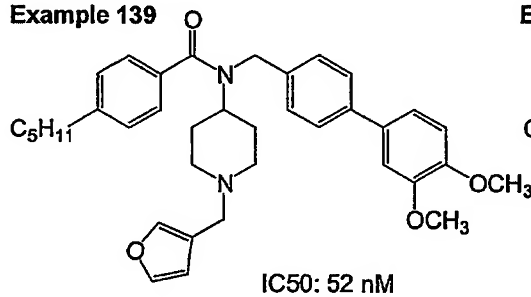
IC50: 39 nM

Example 138



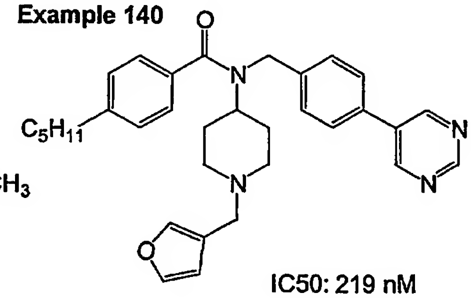
IC50: 77 nM

Example 139



IC50: 52 nM

Example 140

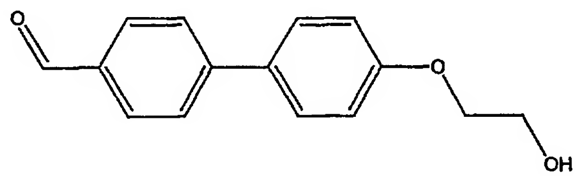


IC50: 219 nM

c) Referential Examples: (e.g. not commercially available starting materials)

Referential Example 1:

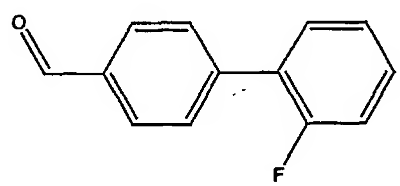
According to typical procedure D), 4-formylbenzeneboronic acid is coupled with 2-(4-bromophenoxy) ethanol to give



4'-(2-Hydroxy-ethoxy)-biphenyl-4-carbaldehyde

Referential Example 2:

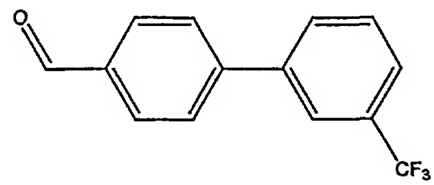
According to typical procedure D), 4-formylbenzeneboronic acid is coupled with 1-bromo-2-fluorobenzene to give



2'-Fluoro-biphenyl-4-carbaldehyde

Referential Example 3:

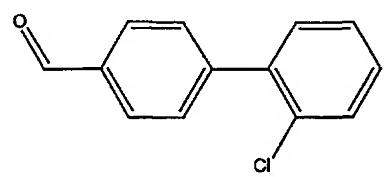
According to typical procedure D), 4-formylbenzeneboronic acid is coupled with 1-bromo-3-trifluoromethylbenzene to give



3'-Trifluoromethylbiphenyl-4-carbaldehyde

Referential Example 4:

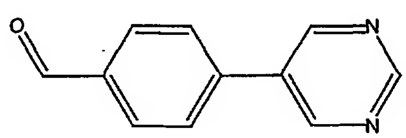
According to typical procedure D), 4-formylbenzeneboronic acid is coupled with 1-bromo-2-chlorobenzene to give



2'-Chlorobiphenyl-4-carbaldehyde

Referential Example 5:

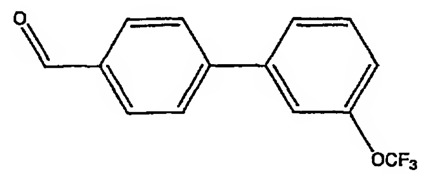
According to typical procedure D), 4-formylbenzeneboronic acid is coupled with 5-bromopyrimidine to give



4-Pyrimidin-5-yl-benzaldehyde

Referential Example 6:

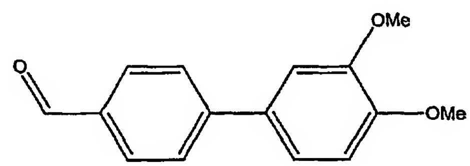
According to typical procedure D), 4-formylbenzeneboronic acid is coupled with 1-bromo-3-(trifluoromethoxy)benzene to give



3'-Trifluoromethoxybiphenyl-4-carbaldehyde

Referential Example 7:

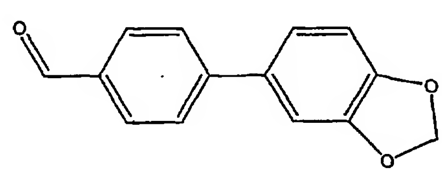
According to typical procedure D), 4-formylbenzeneboronic acid is coupled with 1-bromo-3,4-dimethoxybenzene to give



3',4'-Dimethoxybiphenyl-4-carbaldehyde

Referential Example 8:

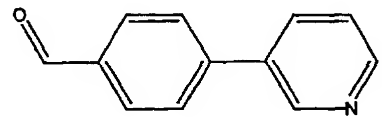
According to typical procedure D), 4-formylbenzeneboronic acid is coupled with 5-bromo-benzo[1,3]dioxole to give



4-Benzo[1,3]dioxol-5-yl-benzaldehyde

Referential Example 9:

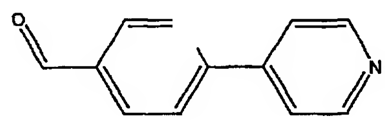
According to typical procedure D), 4-formylbenzeneboronic acid is coupled with 3-bromopyridine to give



4-Pyridin-3-yl-benzaldehyde

Referential Example 10:

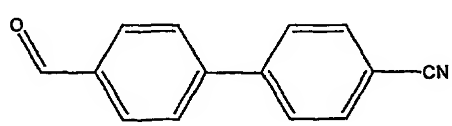
According to typical procedure D), 4-formylbenzeneboronic acid is coupled with 4-bromopyridine to give



4-Pyridin-4-yl-benzaldehyde

Referential Example 11:

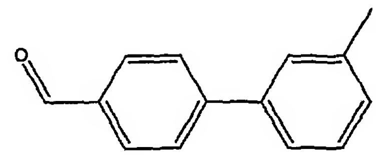
According to typical procedure D), 4-formylbenzeneboronic acid is coupled with 4-bromobenzonitrile to give



4'-Formylbiphenyl-4-carbonitrile

Referential Example 12:

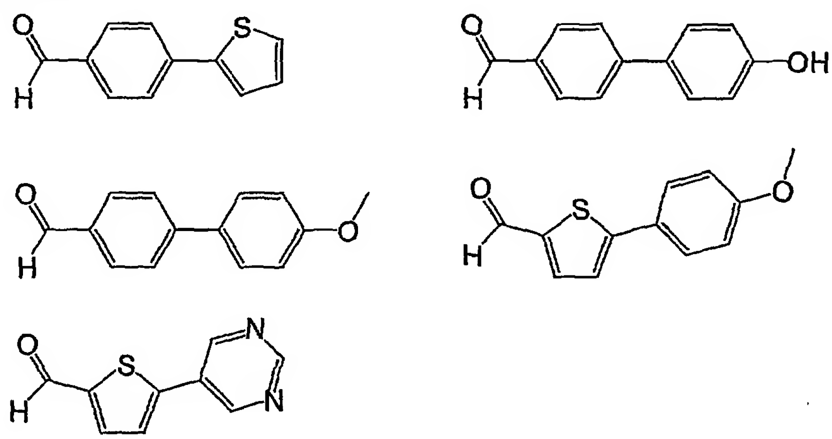
According to typical procedure D), 4-formylbenzeneboronic acid is coupled with 3-bromotoluene to give



3'-Methylbiphenyl-4-carbaldehyde

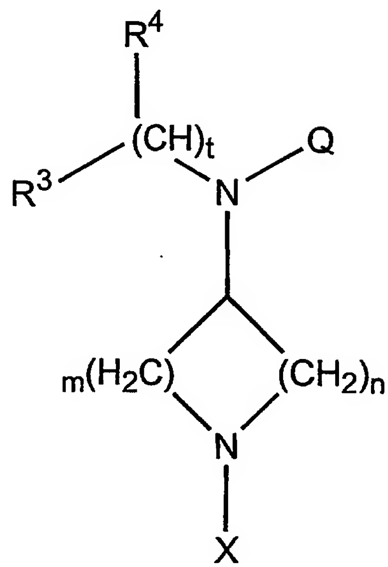
Referential Example 13:

The following biaryl-derivatives could be prepared according to the typical procedure D):



Claims:

1. Compounds of the general **formula I**



General Formula I

wherein

Q represents $-SO_2-R^1$; $-CO-R^1$; $-CO-NH-R^1$; $-CO-N(R^1)(R^2)$; $-CO-OR^1$; $-(CH_2)_p-R^1$; $-(CH_2)_p-CH(R^1)(R^2)$;

X represents $-SO_2-R^1$; $-CO-R^1$; $-CO-NH-R^1$; $-CO-N(R^1)(R^2)$; $-CO-OR^1$; $-(CH_2)_p-R^1$; $-(CH_2)_p-CH(R^1)(R^2)$; hydrogen;

R^1, **R^2** and **R^3** represent lower alkyl; lower alkenyl; aryl; heteroaryl; cycloalkyl; heterocyclyl; aryl-lower alkyl; heteroaryl-lower alkyl; cycloalkyl-lower alkyl; heterocyclyl-lower alkyl; aryl-lower alkenyl; heteroaryl-lower alkenyl; cycloalkyl-lower alkenyl; heterocyclyl-lower alkenyl;

R^4 represents hydrogen; $-CH_2-OR^5$; $-CO-OR^5$;

$\mathbf{R^5}$ represents hydrogen, lower alkyl; cycloalkyl; aryl; heteroaryl; heterocyclyl; cycloalkyl-lower alkyl; aryl-lower alkyl; heteroaryl-lower alkyl; heterocyclyl-lower alkyl;

t represents the whole numbers 0 (zero) or 1, in case t represents the whole number 0 (zero), $\mathbf{R^4}$ is absent;

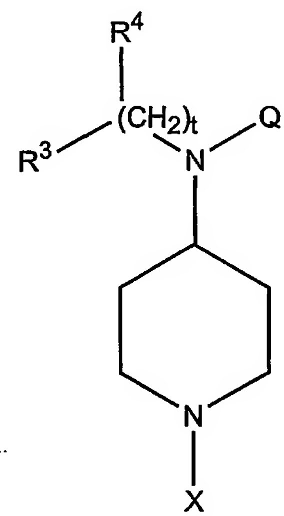
m represents the whole numbers 2, 3 or 4;

n represents the whole numbers 1 or 2;

p represents the whole numbers 0 (zero), 1 or 2;

and pure enantiomers, mixtures of enantiomers, pure diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates and pharmaceutically acceptable salts ereof

2. Compounds of **formula II**



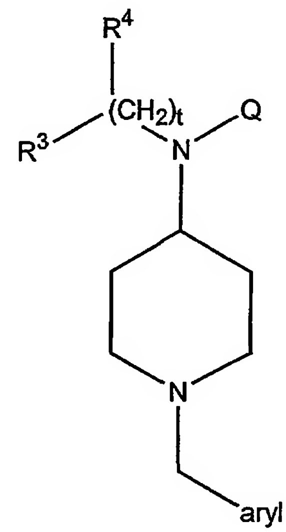
Formula II

wherein

X, Q, t, $\mathbf{R^3}$ and $\mathbf{R^4}$ are as defined in general formula I above

and pure enantiomers, mixtures of enantiomers, pure diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates and pharmaceutically acceptable salts thereof.

3. Compounds of **formula III**



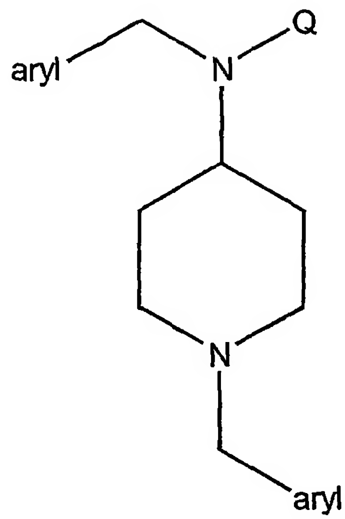
Formula III

wherein

Q, **t**, **R**^{3} and **R**^{4} are as defined in general formula I above

and pure enantiomers, mixtures of enantiomers, pure diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates and pharmaceutically acceptable salts thereof.

4. Compounds of **formula IV**



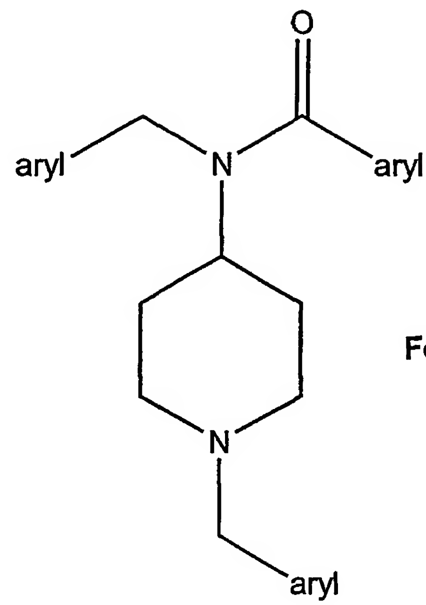
Formula IV

wherein

Q is as defined in general formula I above

and pure enantiomers, mixtures of enantiomers, pure diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates and pharmaceutically acceptable salts thereof.

5. Compounds of **formula V**



Formula V

and pure enantiomers, mixtures of enar...omers, pure diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates and pharmaceutically acceptable salts thereof.

6. A compound as described as end-product in any of the examples 1 to 140.

7. Pharmaceutical compositions containing one or more compounds as claimed in any one of claims 1 to 6 and inert excipients.

8. Pharmaceutical compositions according to claim 7 for treatment of diseases demanding the inhibition of aspartic proteases.

9. Pharmaceutical compositions according to claim 7 for treatment of disorders associated with the role of plasmepsin II and which require selective inhibition of plasmepsin II.

10. Pharmaceutical compositions according to claim 7 for treatment or prevention of malaria.

11. Pharmaceutical compositions according to claim 7 for treatment or prevention of diseases caused by protozoal infection (e.g. Chagas disease, Sleeping sickness etc).

12. Pharmaceutical compositions according to claim 7, which contain aside of one or more compounds of the general formula I a known plasmepsin II, a known HIV protease or a known cathepsin D or E inhibitor.

13. A process for the preparation of a pharmaceutical composition according to any one of claims 8 to 11, characterized by mixing one or more active ingredients according to any one of claims 1 to 6 with inert excipients in a manner known per se.

14. Use of at least one of the compounds of the general formula I for the treatment or prevention of diseases.

15. The invention as herein before described.

INTERNATIONAL SEARCH REPORT

Inte   nal Application No
PCi/EP 01/10272

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D211/58 A61K31/435 A61P33/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BEILSTEIN Data, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 98 05336 A (LO CASTRO STEPHEN ;MARQUIS ROBERT W JR (US); SMITHKLINE BEECHAM CO) 12 February 1998 (1998-02-12) page 23, line 28; claim 1 ---	4-14
A	CARROLL C D ET AL: "Identification of potent inhibitors of plasmodium falciparum plasmepsin II from an encoded statine combinatorial library" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 8, no. 17, 8 September 1998 (1998-09-08), pages 2315-2320, XP004138224 ISSN: 0960-894X the whole document --- -/--	4-14

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 January 2002	16/01/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Lauro, P

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	WO 99 12532 A (HOFFMANN LA ROCHE ;MATILE HUGUES (CH); BUR DANIEL (CH); FISCHLI WA) 18 March 1999 (1999-03-18) page 19; claim 1	4-14
X	N. J. HARPER; C. F. CHIGNELL: "The chemistry and pharmacology of some 4-aminopiperidines and their derivatives" J. MED. CHEM., vol. 7, 1964, pages 729-732, XP001037233 examples 21-23; table I	4,7
X	A. F. CASY; M. R. HUCKSTEP: "Structure-Activity Studies of Fentanyl" J. PHARM. PHARMACOL., vol. 40, 1988, pages 605-608, XP001037232 table 2	4,7
E	WO 01 66521 A (ULDAM A K ;HANSEN E L (DK); ANDERSSON CARL M (DK); CROSTON GLENN () 13 September 2001 (2001-09-13) claim 6	4-14
E	WO 01 81308 A (MADDAFORD SHAWN P ;SLASSI ABDELMALIK (CA); TSE HOI LUN ALLAN (CA);) 1 November 2001 (2001-11-01) * see p. 56 Exp. no. 1.9; p. 56 Exp. no. 1,3; p. 59, Exp. no. 1.29, p. 60 Exp. no. 1.26; p. 61 Exp. no. 1.14, 1.13, 1.12, 1.10, 1.27, 1.28 *	4-14

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-3

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claim(s) may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, a meaningful search over the whole breadth of the claim(s) is impossible. Consequently, the search has been restricted to the compounds of formula (IV).

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 01/10272

Patent document cited in search report		Publication date	Patent family member(s)			Publication date
WO 9805336	A	12-02-1998	AP	865	A	17-08-2000
			AU	711014	B2	07-10-1999
			AU	1270797	A	17-07-1997
			AU	721853	B2	13-07-2000
			AU	3972697	A	25-02-1998
			BG	101712	A	27-02-1998
			BG	103144	A	30-09-1999
			BR	9711044	A	24-10-2000
			CA	2209109	A1	09-05-1997
			CN	1177293	A	25-03-1998
			CN	1232399	A	20-10-1999
			CZ	9900362	A3	14-07-1999
			CZ	9702060	A3	17-02-1999
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			EP	0936912	A1	25-08-1999
			HU	9802488	A2	01-02-1999
			HU	9902409	A2	29-11-1999
			JP	2000516920	T	19-12-2000
			JP	10512300	T	24-11-1998
			NO	973009	A	27-08-1997
			NO	990548	A	07-04-1999
			PL	328877	A1	01-03-1999
			PL	331533	A1	19-07-1999
			SK	16299	A3	10-12-1999
			SK	48198	A3	07-10-1998
			SK	88997	A3	06-05-1998
			TR	9700560	T1	21-11-1997
			TR	9900249	T2	21-04-1999
			WO	9716177	A1	09-05-1997
			WO	9805336	A1	12-02-1998
			US	6274336	B1	14-08-2001
			ZA	9707032	A	04-08-1998
WO 9912532	A	18-03-1999	AU	9740998	A	29-03-1999
			WO	9912532	A2	18-03-1999
WO 0166521	A	13-09-2001	WO	0166521	A1	13-09-2001
WO 0181308	A	01-11-2001	WO	0181308	A2	01-11-2001